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# Bio Research INTERNATIONAL

## Nanoparticle Created For Cancer Therapy

A physicist working to create a luminescent nanoparticle to use in security-related radiation detection may have instead developed a new tool for photodynamic cancer therapy. Wei Chen, professor of physics and co-director of University of Texas (UT) at Arlington (USA; www.uta.edu) Center for Security

*Cont'd on page 5*

## Mass Spectrometry Technology Maps Chemicals as They Migrate into Skin

A mass spectrometry technique gaining acceptance for medical applications such as imaging tumor surfaces can also be used to analyze the migration of small-molecule compounds applied to the skin. Because skin is such a complicated organ, the technology could be a helpful for developing transdermal drugs.

The study's findings were published April 28, 2014, in the *Journal of the American Chemical Society*. Stanford University (Stanford, CA, USA; www.stanford.edu) chemistry Professors Richard N. Zare and Justin Du Bois, postdoc Livia S. Eberlin, graduate student John V. Mulcahy, and colleagues revealed

*Cont'd on page 6*

## Graphene Could Reshape Neurological Treatment

Graphene, a two-dimensional (2D) crystalline allotrope of carbon, may lead to new advances in several areas of neurosurgery, according to a new topic review. Researchers at the University of Illinois College of Medicine (Peoria, USA; www.peoria.medicine.uic.edu) and Invision Health Brain and Spine

*Cont'd on page 7*

# Nature Bank Technique Expands Horizons of Drug Discovery

**Australian researchers have developed an NMR screening process for identifying natural compounds that could lead to widespread development of innovative therapeutic agents. The process is based on investigating an extensive Nature Bank incorporating over 45,000 samples of plants and marine invertebrates, 200,000 semipurified fractions, 3,250 pure compounds and 600 naturally occurring fragments.**

***See article on page 2***

*Image: Prof. Ronald Quinn asserts the new technique could be used to treat a variety of conditions in the future*

*Image: Courtesy of Griffith University*

## Light-Activated Neurons Restore Paralyzed Muscles

A new approach has been developed to synthetically control muscles using light, with the hope of restoring function to muscles paralyzed by disorders such as spinal cord injury and motor neuron disease. The technique involves transplanting specially designed motor neurons created from stem cells into

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## Benchtop Line Provides Automated Sample Decapping, Recapping and Identification

A new line of benchtop devices provides flexible solutions for sample processing, tracking, and security for automated and manual liquid handling workflows.

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## Restoring Effectiveness Of Older Antibiotics

Methicillin-resistant *Staphylococcus aureus* (MRSA), a complex of multidrug-resistant Gram-positive bacterial strains, has proven especially problematic in both hospital and community settings. These bacteria have become drug resistant by deactivating conventional beta-lactam antibiotics, including

*Cont'd on page 6*

## Genetic Brain Disorder Found in Humans

A newly identified genetic disorder linked to the degeneration of the central and peripheral nervous systems in humans, in addition to its the genetic cause, has been reported by researchers. By performing DNA sequencing of more than 4,000 families affected by neurologic difficulties, the

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## INSIDE

*Latest Advances & Applications in:*

# Nature Bank Technique Expands Horizons of Drug Discovery

Australian researchers have developed a new tool for finding natural compounds that could form the foundation of innovative therapeutic agents.

The corresponding author, Prof. Ronald Quinn AM from Griffith University's Eskitis Institute for Drug Discovery (Brisbane, Australia; www.griffith.edu.au/science-aviation/eskitis-institute), reported that testing the new process on a marine sponge had delivered not only validation that the system is successful, but also a potential lead in the fight against Parkinson's disease. "We have found a new screening method which allows us to identify novel molecules drawn from nature to test for biological activity," Prof. Quinn said. "As it happens, the first new compound we discovered through this process has demonstrated a response in Parkinson's disease cells."

The findings were published online April 15, 2014, in the chemistry journal *Angewandte Chemie*. The first author Dr. Tanja Grkovic said the screening process involves nuclear magnetic resonance (NMR) spectroscopy; a highly sensitive instrument through which it is possible to see natural products weighing as little as 20 micrograms. "When you are searching for nature-derived molecules, the jackpot is finding something that nobody has ever seen before and rather than just a variation on a known theme," Dr. Grkovic said. "We began the project by selecting 20 marine sponge samples randomly from Griffith University's Nature Bank facility and using the NMR technique trying to visualize all the small molecules which could meet the requirements for a potential new drug. "The idea was to look at patterns of data and identify unusual or unique sets. We followed one such pattern and isolated a natural product with a novel skeleton which has turned out to be a molecule which was completely unknown previously."

The Griffith Nature Bank is a novel drug discovery resource based on natural products found in China, Australia, and Papua New Guinea. It comprises more than 45,000 samples of plants and marine invertebrates, 200,000 semipurified fractions, 3,250 pure compounds and over 600 naturally occurring fragments. This NMR screening process provides a new way of searching all those natural samples stored in the Griffith Nature Bank and uncovering the potential biological activity of the compounds within them.

Deputy director of the Eskitis Institute and coauthor of the paper, Assoc. Prof. George Mellick, is a specialist researcher in neurodegenerative diseases such as Parkinson's disease. He is excited by the research prospects this new molecule may provide. "What is very intriguing about this novel natural product is that, while we have found it has an effect on cells sourced from a Parkinson's patient, it showed a different biological activity on cells from healthy individuals," Assoc. Prof. Mellick said. "This provides us with a new tool to study the fundamental biology of Parkinson's and to get a better understanding of the cellular processes involved in the development of this disease."

The Parkinson's response is only the beginning, according to the scientists. "This new research technique opens the door to unlimited opportunities, both in terms of chemistry and biology research at Eskitis, as we continue the search for new therapies against disease," Prof. Quinn said.

# Light-Activated Neurons Restore Paralyzed Muscles

*cont'd from cover*

damaged nerve branches. These motor neurons are devised to react to pulses of blue light, allowing researches to customize muscle control by adjusting the duration, intensity, and frequency of the light pulses.

In the study published April 2014 in *Science*, scientists from University College London (UCL; UK; www.ucl.ac.uk) and King's College London (UK; www.kcl.ac.uk) demonstrated the technology in lab mice in which the nerves that supply muscles in the hind legs were injured. They showed that the transplanted stem cell-derived motor neurons grew along the injured nerves to connect effectively with the paralyzed muscles, which could then be controlled by pulses of blue light.

"Following the new procedure, we saw previously paralyzed leg muscles start to function," noted Prof. Linda Greensmith of the MRC Center for Neuromuscular Diseases at UCL's Institute of Neurology, who co-led the study. "This strategy has significant advantages over existing techniques that use electricity to stimulate nerves, which can be painful and often results in rapid muscle fatigue. Moreover, if the existing motor neurons are lost due to injury or disease, electrical stimulation of nerves is rendered useless as these too are lost."

Muscles are typically controlled by motor neurons, which are specialized nerve cells within the brain and spinal cord. These neurons relay signals from the brain to muscles to initiate motor functions such as walking, standing and even breathing. However, motor neurons can become damaged in motor neuron disease or following spinal cord injuries, causing permanent loss of muscle function resulting in paralysis.

"This new technique represents a means to restore the function of specific muscles following paralyzing neurological injuries or disease," clarified Prof. Greensmith. "Within the next five years or so, we hope to undertake the steps that are necessary to take this ground-breaking approach into human trials, potentially to develop treatments for patients with motor neuron disease, many of whom eventually lose the ability to breathe, as their diaphragm muscles gradually become paralyzed. We eventually hope to use our method to create a sort of optical pacemaker for the diaphragm to keep these patients breathing."

The light-responsive motor neurons that made the technique possible were created from stem cells by Dr. Ivo Lieberam of the MRC Center for Developmental Neurobiology, King's College London. "We custom-tailored embryonic stem cells so that motor neurons derived from them can function as part of the muscle pacemaker device," said Dr. Lieberam, who co-led the study. "First, we equipped the cells with a molecular light sensor. This enables us to control motor neurons with blue light flashes. We then built a survival gene into them, which helps the stem-cell motor neurons to stay alive when they are transplanted inside the injured nerve and allows them to grow to connect to muscle."

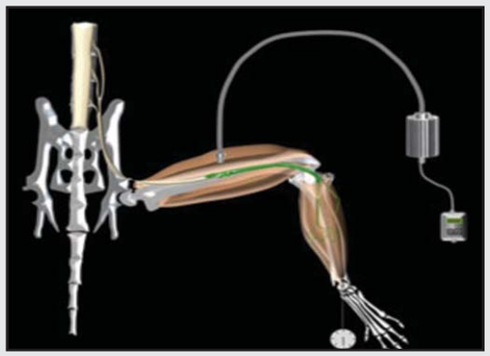

*Image: A new technique using light on stem cell-derived motor neurons could potentially restore function to paralyzed muscles (Photo courtesy of Dr. Barney Bryson / University College London Institute of Neurology).*

# Genetic Brain Disorder Found in Humans

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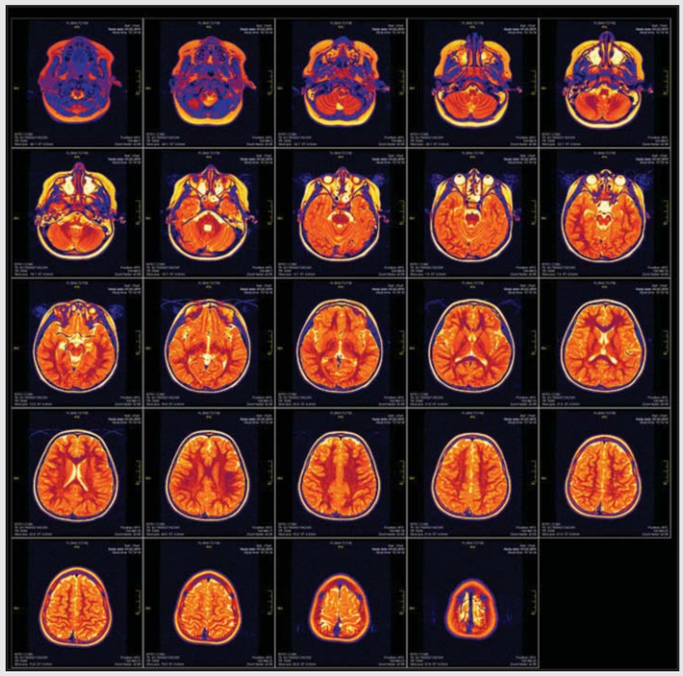

two teams of investigators independently discovered that a disease marked by reduced brain size and sensory and motor defects is caused by a mutation in a gene called CLP1 (cleavage and polyadenylation factor I), which is known to regulate tRNA metabolism in cells.

The news findings were reported in the April 24, 2014 issue of the journal *Cell*. The findings were made by two independent but collaborative scientific teams, one based primarily at Baylor College of Medicine (Houston, TX, USA; www.bcm.edu) and the Austrian Academy of Sciences (Vienna, Austria; www.oeaw.ac.at), the other at the University of California (UC), San Diego School of Medicine (USA; http://ucsd.edu), the Academic Medical Center (AMC; Amsterdam, The Netherlands; www.amc.nl), and Yale University School of Medicine (New Haven, CT, USA; http://medicine.yale.edu).

Clues into this rare disorder, according to the researchers, may have important implications for the future treatment of more common neurologic disorders. "What we found particularly striking, when considering the two studies together, is that this is not a condition that we would have been able to separate from other similar disorders based purely on patient symptoms or clinical features," said Joseph G. Gleeson, MD, Howard Hughes Medical Institute investigator, professor in the UC San Diego departments of neurosciences and pediatrics and at Rady Children's Hospital-San Diego, a research affiliate of UC San Diego. "Once we had the gene spotted in these total of seven families, then we could see the common features. It is the opposite way that doctors have defined diseases, but represents a transformation in the way that medicine is practiced."

Each child assessed was affected by undiagnosed neurological problems. All of the children were discovered to carry a mutation in the CLP1 gene and displayed the same symptoms, such as brain malformations, intellectual disabilities, seizures and sensory and motor defects. A similar pattern emerged in both studies, one led by Gleeson, with Murat Gunel, MD, of the Yale University School of Medicine and Frank Baas, PhD, of the Academic Medical Center in the Netherlands, and the other by Josef Penninger and Javier Martinez of the Austrian Academy of Sciences, collaborated with James R. Lupski, MD, PhD, of the Baylor College of Medicine.

"Knowing fundamental pathways that regulate the degeneration of neurons should allow us to define new pathways that, when modulated, might help us to protect motor neurons from dying, such as in Lou Gehrig's disease," said Dr. Penninger, scientific director of the Institute of Molecular Biotechnology of the Austrian Academy of Sciences.

The CLP1 protein plays an important role in generating mature, functional molecules called transfer RNAs (tRNAs), which shuttle amino acids to cellular subunits called ribosomes for assembly into proteins. Mutations affecting molecules involved in producing tRNAs have been implicated in human neurological disorders, such as pontocerebellar hypoplasia (PCH), a currently incurable neurodegenerative disease affecting children. Although CLP1 mutations have been linked to neuronal death and motor defects in mice, the role of CLP1 in human disease was not known until now.

These scientists performed DNA sequencing on children with neurologic difficulties. Seven out of the more than 4,000 families studied shared an identical CLP1 mutation, which was associated with seizures, motor defects, speech impairments, brain atrophy, and neuronal death.

Dr. Bass, from the AMC, noted that the neurological condition represents a new form of PCH. "Identification of yet another genetic cause for this neurodegenerative disorder will allow for better genetic testing and counseling to families with an affected child," he said.

In a published paper in 2013, Dr. Gleeson and colleagues identified a different gene mutation for a particularly severe form of PCH, and reported early evidence that a nutritional supplement might one day be able to prevent or reverse the condition.

*Image: Brain MRI slide. A newly identified genetic disorder associated with degeneration of the central and peripheral nervous systems in humans, along with the genetic cause, has been discovered by researchers (Photo courtesy of Fotolia).*

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# Nanoparticle Created For Cancer Therapy

*cont'd from cover*

Advances Via Applied Nanotechnology, was testing a copper-cysteamine (Cu-Cy) complex created in his lab when he discovered mysterious decreases in its luminescence, or light emitting power, over a time-lapse exposure to X-rays. Researching further, he discovered that the nanoparticles, called Cu-Cy, were losing energy as they emitted singlet oxygen – a toxic byproduct used to damage cancer cells in photodynamic therapy.

Because Prof. Chen also is leading federally funded cancer research, he knew he had found something unique. Testing revealed that the Cu-Cy nanoparticles, combined with X-ray exposure, significantly slowed tumor growth in lab studies. "This new idea is simpler and better than previous photodynamic therapy methods. You don't need as many steps. This material alone can do the job," Prof. Chen said. "It is the most promising thing we have found in these cancer studies and we've been looking at this for a long time."

Prof. Chen's research will be published in the August 2014 edition of the *Journal of Biomedical Nanotechnology*. The article was published online April 2014. The University has also filed a provisional patent application on the new complex.

Photodynamic therapy (PDT) harms cancer cells when a photosensitizer introduced into tumor tissue produces toxic singlet oxygen after being exposed to light. In some studies, this light exposure is done through use of visible or near-infrared lasers. Others have found more success by also introducing luminescent nanoparticles into the tumor. Researchers activate the luminescent nanoparticle with near-infrared light or X-rays, which in turn activates the photosensitizer.

Both techniques have limitations for treating deep tissue cancers. They are either ineffective or the light source needed to activate them does not penetrate deep enough. Prof. Chen reported that X-ray-inducible Cu-Cy particles surpass current photosensitizers because the X-rays can penetrate deep into tissue. Furthermore, Cu-Cy nanoparticles do not need other photosensitizes to be effective so the treatment is more convenient, efficient and cost-effective.

"Dr. Chen's commitment to his work in cancer-related therapy, as well as his work in the area of homeland security, demonstrates the wide-ranging applications and great value of basic science research," said Carolyn Cason, vice president for research at UT Arlington. "These advances have the potential to change the way some cancers are treated and make therapy more effective – a benefit that would be boundless."

Prof, Chen's team assessed the Cu-Cy on human breast and prostate cancer cells in the lab and found it to be an effective treatment when combined with X-ray exposure. In one esperiment, for example, a tumor treated with Cu-Cy injection and X-ray exposure stayed virtually the same size over a 13-day period while a tumor without the full treatment grew by three times.

Another benefit of the new nanoparticle is a low toxicity to healthy cells. Furthermore, Cu-Cy's intense photoluminescence and X-ray luminescence can be employed for cell imaging, according to the scientists. Details of the crystal structure and optical characteristics of the new complex are slated for publication in the *Journal of Materials Chemistry*. Prof. Chen reported that additional research would include reducing the size of the Cu-Cy nanoparticle to make it more easily absorbed in the tumor tissue. "For cancer, there is still no good solution yet. Hopefully this nanoparticle can provide some possibilities," he said.

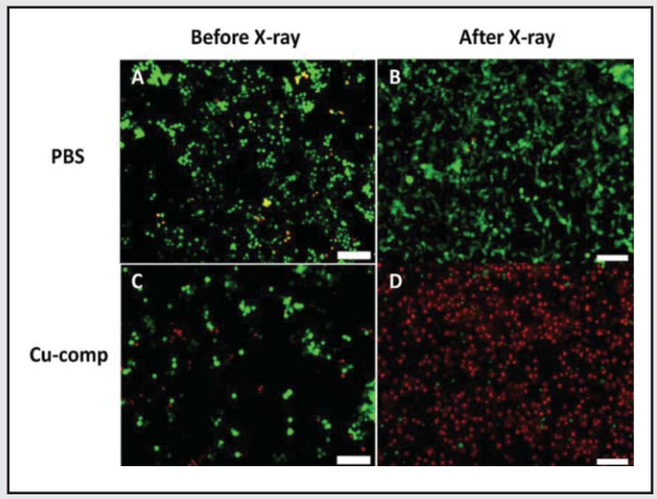


*Image: The X-ray destruction of human breast cancer cells using Cu-Cy particles. The images show the live cancer cells stained green and the dead cells stained red (Photo courtesy of Wei Chen / UT Arlington).*

# Restoring Effectiveness of Older Antibiotics

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penicillins, cephalosporins, and carbapenems, through various mechanisms, resulting in increased mortality rates and hospitalization costs. Microbiologists at the University of South Carolina (Columbia, SC, USA; www.sc.edu) introduced a class of charged metallopolymers that exhibit synergistic effects against MRSA by efficiently inhibiting activity of beta-lactamase and effectively lysing bacterial cells. The metallopolymer by itself even demonstrated antimicrobial properties, lysing bacterial cells while leaving human red blood cells unaffected. By a variety of measures, the polymer was found to be nontoxic to human cells in laboratory tests.

The beta-lactam structure in a molecule is something that many bacteria are adverse to. It greatly hinders their ability to reproduce by cell division, and so chemists have for years spent time making molecules that all contain the beta-lactam structural motif. One of the most effective bacterial defenses is an enzyme called beta-lactamase, which chews up the beta-lactam structure. Some bacteria, such as MRSA, have developed the ability to biosynthesize and release beta-lactamase when needed. It is a devastating defense because it is so general, targeting the common structural motif in all of the many beta-lactam antibiotics.

The interdisciplinary team also showed that the antimicrobial effectiveness of the four beta-lactams studied in detail was enhanced by the polymer. They prepared a cobaltocenium metallopolymer that greatly slowed the destructiveness of beta-lactamase on a model beta-lactam molecule (nitrocefin). The enhancement was modest against two strains, but very pronounced with the hospital-associated strain of MRSA (HA-MRSA). The four antibiotics penicillin-G, amoxicillin, ampicillin, and cefazolin, were protected from beta-lactamase hydrolysis via the formation of unique ion-pairs between their carboxylate anions and cationic cobaltocenium moieties.

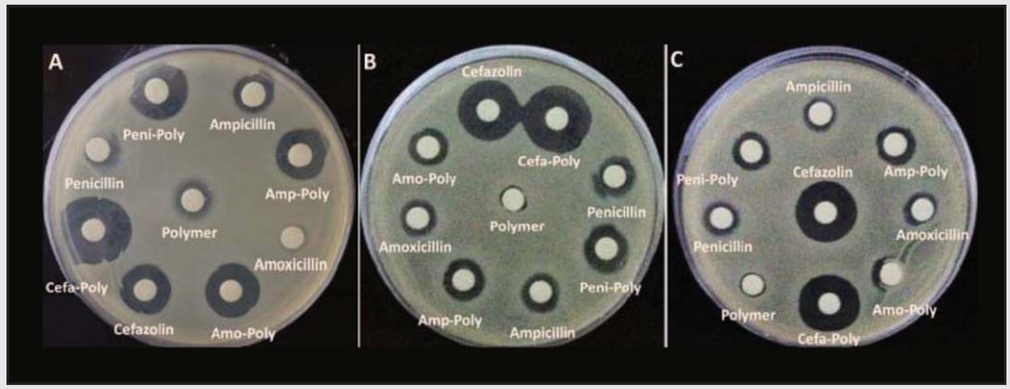


*Image: Conjugates of a beta-lactam antibiotic with the team's metallopolymer had enhanced antimicrobial properties compared with the antibiotic alone. The effect was particularly striking with hospital-associated MRSA (left) (Photo courtesy of the University of South Carolina).*

Chuanbing Tang, PhD, the lead author of the study said, "Instead of developing new antibiotics, here we ask the question, can we recycle the old antibiotics? With traditional antibiotics like penicillin G, amoxicillin, and ampicillin and so on, can we give them new life? In the USA every year, around 100,000 patients die of bacteria-induced infections, and the problem is increasing because bacteria are building resistance. It's a really, really big problem, not only for individual patients, but also for society." The study was published on March 17, 2014, in the *Journal of the American Chemical Society.*

# Mass Spectrometry Technology Maps Chemicals as They Migrate into Skin

*cont'd from cover*

that desorption electrospray ionization-mass spectrometry (DESI-MS) imaging has many advantages over other approaches that require complicated preparation of skin samples.

Moreover, DESI-MS imaging can be performed under ambient settings, instead of in a vacuum condition, as other MS methods require. Furthermore, test compounds do not have to be radioactively labeled or tagged with unwieldy dye molecules that could affect the compounds' normal migration through skin. "That's why this method is very appealing," said Mark R. Prausnitz, a chemical and biomolecular engineering professor who heads the Laboratory for Drug Delivery at Georgia Institute of Technology (Atlanta, GA, USA).

DESI-MS was developed 10 years ago and involves spraying charged solvent droplets at a surface. Backsplash droplets containing dissolved molecules are then captured and examined using a mass spectrometer. The technology has been used for medical applications such as imaging drugs in tissue samples.

The Stanford scientists chose a number of small molecules that change sodium channels in skin cells, including lidocaine and a shellfish toxin. They applied them to the surface of skin samples and were able to track the compounds' migration to a depth of 1.2 mm.

Such studies of drug migration are required to enlarge the limited selection of transdermal drugs, according to Prof. Prausnitz. Only approximately 30 agents, such as nicotine, have transdermal versions. The drugs must be small, lipophilic, and effective at a low dose. With this newly adapted tool, however, scientists could more readily study methods to enhance skin permeation, Prof. Prausnitz reported. "We're very interested in the pathway – which part of the skin did the drug go through?"

# Benchtop Line Provides Automated Sample Decapping, Recapping and Identification

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The LabElite line from Hamilton Storage Technologies (Franklin, MA, USA; www.hamilton-storage.com) offers laboratories an easy and efficient way to automatically process and track samples while ensuring sample integrity. LabElite devices quickly process all common labware types, providing a flexible solution for optimizing workflows. Three models are available to meet a user's application, throughput, and sample tracking needs.

The all-in-one LabElite I.D. Capper enables labs to combine decapping/recapping and high-speed barcode reading within one device without additional user interaction. The I.D. Capper is specifically designed to reduce sample contamination and assist with sample tracking during end-to-end automated liquid-handling processing. The I.D. Capper includes all the new features and benefits standard to the other LabElite devices.

When sample tracking is not required, the next-generation LabElite DeCapper is available for decapping and recapping tubes in 48-cryovial or 96-microtube racks. A new feature can automatically move the racks from portrait to landscape formats for processing. Additionally, an innovative "secure mode" provides sample security by decapping and recapping only one row at a time, minimizing the time a tube is open and eliminating the risk of cross contamination. This feature also enables the rows to be paused for "point-of-use" pipetting between capping and recapping, which is very useful for manual workflows. The DeCapper can process all common tubes, including Matrix, FluidX, Greiner Bio-One, Micronic, Nunc, and Corning, with internal and external thread caps.

For labs with manual workflows that need an efficient, high-speed 2D barcode reader for tube racks, the LabElite I.D. Reader is an ideal choice. This device decodes multiple types of labware including 2D barcoded tubes in all common 12-, 24-, 48-, 96- and 384-tube racks including honeycomb-shaped racks, providing complete sample tracking during processing. In addition, the reader can identify racks that are labeled with a 2D barcode on the bottom. The technology uses high-speed decoding algorithms and parallel processing, which provides the fastest run times currently available. A 96-tube rack runs in less than 3 seconds and a 384-tube rack in less than 5 seconds. Optional 1D barcode reading of the rack label is also available. The I.D. Reader supports all common tubes, including Matrix, FluidX, Greiner Bio-One, Micronic, Nunc, Corning, Matrical, WHEATON, ABgene, and REMP.

The LabElite I.D. Capper, DeCapper and I.D. Reader are for research only, not for use in clinical diagnostic procedures.

# Graphene Could Reshape Neurological Treatment

*cont'd from cover*

Center (Williamsville, NY, USA; www.invisionhealth.com) argue that neurosurgeons could use graphene-based metamaterials, which possess unique optical, thermal, mechanical, electronic, and quantum properties, to encourage the development of high-performance, lightweight, and malleable electronic devices, ultracapacitors, optical modulators, molecular biodevices, organic photovoltaic cells, lithium-ion microbatteries, frequency multipliers, quantum dots, and integrated circuits.

According to the review, these potential breakthroughs in graphene biomedical technology over the next few decades could significantly impact several areas of neurosurgery, including neuro-oncology, neurointensive care, neuroregeneration research, peripheral nerve surgery, functional neurosurgery, and spine surgery. The review also provides an introduction to the main properties of graphene and discusses future perspectives of ongoing frontline investigations of graphene, with special emphasis on research fields that are expected to substantially impact experimental and clinical neurosurgery. The topic review was published in the May 2014 issue of *Neurosurgery*.

"While graphene has been shown to be biocompatible, more basic research is needed to examine the long-term biological effects of graphene implants and to answer other important clinical questions," concluded study authors Tobias Mattei, MD, and Azeem Rehman, BSc. "Increased awareness of the ongoing frontline research on graphene may enable the neurosurgical community to properly take advantage of the technological applications such a new metamaterial may offer."

Graphene is a monolayer atomic-scale honeycomb lattice of carbon atoms which combines the greatest mechanical strength ever measured in any material (natural or artificial) with very light weight and high elasticity. Graphene has unique optical and photothermal properties which allow it to release energy in the form of heat in response to light input; it also has very high electrical conductivity. The high surface area allows bioconjugation with common biomolecules. Andre Geim and Kostya Novoselov of the University of Manchester (United Kingdom) were awarded the Nobel Prize in Physics in 2010 for its development.

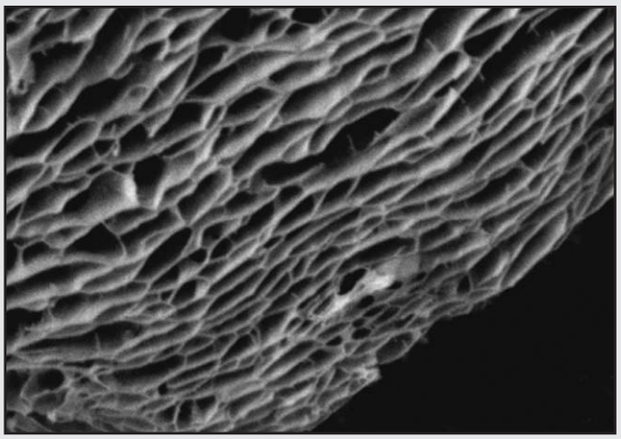


*Image: A close-up view of graphene oxide fiber structure, which may lead to advances in neurosurgery (Photo courtesy of John Hewitt).*

# Transforming Methylated Nucleic Acids into Prostate Tumor Biomarkers

High quality oligonucleoside reagents and detection kits are facilitating research on methylated DNA and its relation to the molecular mechanisms that drive development of prostate cancer.

In the March 31, 2014, online edition of the Integrated DNA Technologies (Coralville, IA, USA; www.idtdna.com) newsletter *DECODED*, Dr. Antoinette Perry, senior research fellow at the Institute of Molecular Medicine (Dublin, Ireland; www.tcd.ie/IMM), described how use of materials supplied by Integrated DNA Technologies (IDT) facilitated her research team's study of prostate cancer.

Research in Dr. Perry's laboratory is directed at understanding how changes in DNA methylation of coding and non-coding RNA genes are involved in driving prostate carcinogenesis. The investigators exploit specific epigenetic changes for early, noninvasive detection of aggressive prostate cancer. In the process, they hope to develop predictive epigenetic biomarkers – focusing both on circulating free nucleic acids and exosomes – that can be quantified by simple, liquid biopsy. Ultimately, they hope to use these biomarkers to develop a noninvasive test that will distinguish high-risk from lower-risk prostate tumors.

Integrated DNA Technologies is one of the largest suppliers of custom nucleic acids in the United States, serving academic, government, and commercial researchers in biotechnology, clinical diagnostics, and pharmaceutical development.

# Aspirin Use for Heart Disease Prevention May Benefit Those with Coronary Artery Calcium Deposits

A recent study found that taking aspirin to prevent heart disease benefits individuals with high coronary artery calcium (CAC) scores but can actually cause damage from bleeding in individuals with low levels of coronary artery calcium.

An individual's CAC score is determined by using computerized tomography (CT) to scan the coronary blood vessels. Calcium deposits show up as bright white spots on the scan.

Investigators at the Minneapolis Heart Institute (MN, USA; www.mplsheart.com) monitored 4,229 individuals participating in the Multi-Ethnic Study of Atherosclerosis (MESA) at six centers in the USA. Participants had no known CVD (cardiovascular disease) or diabetes, were not on aspirin therapy, and were followed for approximately seven years.

Results revealed that participants with elevated CAC scores (greater than 100) were two to four times more likely to benefit from aspirin therapy than to be harmed, even if they did not qualify for aspirin use according to current American Heart Association guidelines. Conversely, MESA participants with no calcified plaque (CAC score = zero) were two to four times more likely to be harmed by aspirin use than to benefit.

"We estimate that individuals with significant plaque buildup in the arteries of the heart are much more likely to prevent a heart attack with aspirin use than to suffer a significant bleed," said first author Dr. Michael D. Miedema, a preventative cardiologist at the Minneapolis Heart Institute. "On the opposite end of the spectrum, if you do not have any calcified plaque, our estimations indicate that use of aspirin would result in more harm than good, even if you have risk factors for heart disease such as high cholesterol or a family history of the disease."

"A CAC score of zero is associated with a very low risk of having a heart attack. That means individuals with a score of zero may not benefit from preventive medications, such as aspirin as well as the cholesterol-lowering statin medications. Approximately 50% of middle-aged men and women have a CAC score of zero, so there is a potential for this test to personalize the approach to prevention and allow a significant number of patients to avoid preventive medications, but we need further research to verify that routine use of this test is the best option for our patients."

The study was published in the May 6, 2014, online edition of the journal *Circulation: Cardiovascular Quality and Outcomes*.

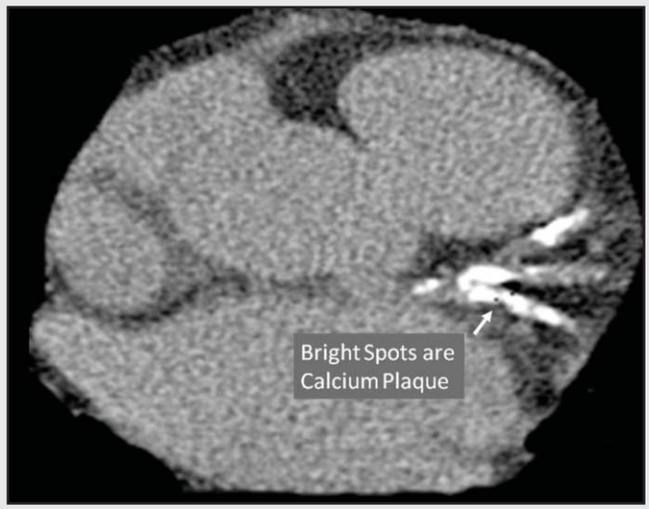



*Image: A computed tomography (CT) scan showing calcium that has built up in the heart (Photo courtesy of the Minneapolis Heart Institute).*

# Monoclonal Antibody Blocks B-Cell Receptor and Eases Leukemia Burden in Mouse Model

Blocking the B-cell-activating factor receptor (BAFF-R) on leukemia cells has been suggested as a new approach for treating an acute, chemotherapy-resistant form of childhood leukemia.

Acute lymphoblastic leukemia (ALL) is characterized by an excessive amount of white blood cell precursors (B-cell lymphoblasts) in the blood and bone marrow. B-cell lineage ALL (pre-B ALL) accounts for 80% to 85% of childhood ALL.

BAFF-R is encoded in humans by the TNFRSF13C (tumor necrosis factor receptor superfamily member 13C) gene. BAFF enhances B-cell survival in vitro and is a regulator of the peripheral B-cell population. Overexpression of BAFF in mice results in mature B-cell hyperplasia and symptoms of systemic lupus erythematosus (SLE). Also, some SLE patients have increased levels of BAFF in their serum. Therefore, it has been proposed that abnormally high levels of BAFF may contribute to the pathogenesis of autoimmune diseases by enhancing the survival of autoreactive B cells. The protein encoded by the TNFRSF13C gene is a receptor for BAFF and is a type III transmembrane protein containing a single extracellular cysteine-rich domain.

It is thought that BAFF-R is the principal receptor required for BAFF-mediated mature B-cell survival. Since BAFF-R is expressed on precursor pre-B ALL cells but not on their pre-B normal counterparts, selective killing of ALL cells is possible by targeting this receptor.

Investigators at the University of Southern California (USA; www.usc.edu) tested a novel humanized anti–BAFF-R monoclonal antibody in a study carried out on leukemia cell cultures and in an immunodeficient mouse transplant model.

They reported in the May 13, 2014, online edition of the journal *Molecular Cancer Therapeutics* that the antibodies significantly stimulated natural killer cell-mediated killing of different human patient-derived ALL cells. Moreover, incubation of such ALL cells with these antibodies stimulated phagocytosis by macrophages. When this was tested in the immunodeficient transplant model, mice that were treated with the antibody had a significantly decreased leukemia burden in bone marrow and spleen.

"We have now demonstrated that BAFF-R is a strong potential therapeutic target for treating chemotherapy-resistant leukemia cells, without damaging healthy cells," said senior author Dr. Nora Heisterkamp, professor of research, pediatrics, and pathology at the University of Southern California. "We found that human pre-B ALL cells could be even further reduced when the anti-BAFF-R antibody was combined with chemotherapy or another therapeutic agent. We are looking at a potential one, two punch."

# Novel Approach Simplifies Complex Sugars on Protein-Based Biotech Medicines

A team of biotech medicine developers has established a cell-based production method that reduces the complexity of the sugars (glycans) expressed on protein-based drugs.

Heterogeneity in the N-glycans on therapeutic proteins causes difficulties for protein purification and process reproducibility and can lead to variable therapeutic efficacy. This heterogeneity arises from the multistep process of mammalian complex-type N-glycan synthesis.

Investigators at, Ghent University (Belgium; www.ugent.be) recently described a novel glycoengineering strategy that they called GlycoDelete, which used a fungal enzyme to shorten the Golgi N-glycosylation pathway in mammalian cells.

They wrote in the April 20, 2014, online edition of the journal *Nature Biotechnology* that this shortening resulted in the expression of proteins with small, sialylated trisaccharide N-glycans and reduced complexity compared to native mammalian cell glycoproteins. GlycoDelete engineering did not interfere with the functioning of N-glycans in protein folding, and the physiology of cells modified by GlycoDelete was similar to that of wild-type cells. This strategy for reducing N-glycan heterogeneity on mammalian proteins could lead to more consistent performance of therapeutic proteins and modulation of biopharmaceutical functions.

Senior author Dr. Nico Callewaert, professor of medical biotechnology at Ghent University, said, "This technology has allowed us to solve an old biotech problem. Since the 1990s, nearly everyone has been working to make the sugar synthesis in biotech production cells as similar to human cells as possible. This is a very difficult task, because there are so many steps in this synthesis pathway. We have been able to create a detour in this synthesis pathway in a fairly simple manner, making the pathway much shorter and simpler."

# Melanoma Triggered by Deficit of Retinoid-X-Receptors in Melanocytes

Cancer researchers have linked the development of the deadly skin cancer melanoma to depressed expression in melanocytes of the type II nuclear receptors Retinoid-X-Receptor alpha (RXRalpha) and Retinoid-X-Receptor beta (RXRbeta).

Melanoma is the deadliest form of skin cancer. It derives from melanocytes, the melanin-producing cells of the skin, which give the skin its tone in addition to protecting it from harmful effects of ultraviolet radiation (UVR). Changes in the skin microenvironment, such as signaling from other cell types, can influence melanoma progression. While several key genes in melanoma development have been identified, the underlying mechanisms are complex; different combinations of mutations can result in melanoma formation and genetic profiles of tumors can vary greatly among patients.

Retinoid X receptors (RXRs) are nuclear receptors that mediate the biological effects of retinoids (vitamin A derivatives) by their involvement in retinoic acid-mediated gene activation. These receptors function as transcription factors by binding as homodimers or heterodimers to specific sequences in the promoters of target genes. The protein encoded by this gene is a member of the steroid and thyroid hormone receptor superfamily of transcriptional regulators.

Since expression of RXRalpha disappears during melanoma progression in humans, investigators at Oregon State University (Corvallis, USA; www.oregonstate.edu) developed a tissue-specific gene ablation strategy to characterize the role of these type II nuclear receptors in melanocytes to control UVR-induced skin immune responses and cell survival.

They reported in the May 8, 2014, online edition of the journal *PLoS Genetics* that melanocytes in mice with melanocyte-specific ablation of RXRalpha and RXRbeta attracted fewer IFN-gamma (interferon-gamma) secreting immune cells than in wild-type mice following acute UVR exposure, via altered expression of several chemoattractive and chemorepulsive chemokines/cytokines. Reduced IFN-gamma in the microenvironment altered UVR-induced apoptosis, and due to this, the survival of surrounding dermal fibroblasts was significantly decreased in mice lacking RXRalpha/beta.

These results emphasized a novel immunomodulatory role for melanocytes in controlling survival of neighboring cell types besides controlling their own, and identified RXRs as potential targets for therapy against UV induced melanoma.

"We believe this is a breakthrough in understanding exactly what leads to cancer formation in melanoma," said senior author Dr. Arup Indra, associate professor of pharmacology at Oregon State University. "We have found that some of the mechanisms which ordinarily prevent cancer are being switched around and actually help promote it. When there is not enough RXR, the melanocytes that exist to help shield against cancer ultimately become part of the problem. It is routine to have genetic damage from sunlight, because normally those cells can be repaired or killed if necessary. It is the breakdown of these control processes that result in cancer, and that happens when RXR levels get too low. It is quite possible that a new and effective therapy can now be developed, based on increasing levels of RXR."

*Image: Arup and Gitali Indra are urgently seeking, and beginning to find, clues to predicting, preventing and stopping melanoma before it spreads (Photo courtesy of Karl Maasdam / Oregon State University College of Pharmacy).*

# Genomic Studies Reveal Links Between Prostate Cancer and Cardiovascular Disease

A large-scale statistical evaluation of genomic studies linked to either prostate cancer (PCA) or cardiovascular disease (CVD) risk identified 17 genetic loci that link prostate cancer to risk of developing CVD.

Investigators at Oslo University (Norway; www.uio.no) and their colleagues at the University of California, San Diego (USA; www.ucsd.edu) applied a genetic epidemiology method based on conjunction false discovery rate (FDR) that combined summary statistics from different genome-wide association studies (GWAS), and allowed identification of genetic overlap between two phenotypes. FDR is a statistical method used in multiple hypotheses testing to correct for multiple comparisons. In a list of findings, FDR procedures are designed to control the expected proportion of incorrectly rejected null hypotheses.

The investigators evaluated summary statistics from large, multicenter GWA studies of PCA (n = 50,000) and CVD risk factors (n = 200,000). CVD risk factors included triglycerides (TG), low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, systolic blood pressure, body mass index, waist-hip ratio, and type II diabetes.

Results published in the April 30, 2014, online edition of the *International Journal of Epidemiology* revealed that the strongest association between PCA and CVD risk was conditional on LDL and TG. In contrast, the investigators found only weak enrichment conditional on HDL or conditional on the other traits investigated. Conjunction FDR identified altogether 17 loci; 10 loci were associated with PCA and LDL, three loci were associated with PCA and TG and additionally four loci were associated with PCA, LDL, and TG jointly.

"It is fair to say that risk relationships of various sorts have been proposed between prostate cancer and cardiovascular disease, although not comorbidity per se," said contributing author Dr. Ian G. Mills, researcher in the prostate cancer group at the University of Oslo. "There is a lack of consistency across cohorts, however, in size and direction of effects, depending on cardiovascular risk factor considered. The significant risk association with LDL cholesterol and triglycerides versus the other traits at a genetic level was novel and unexpected."

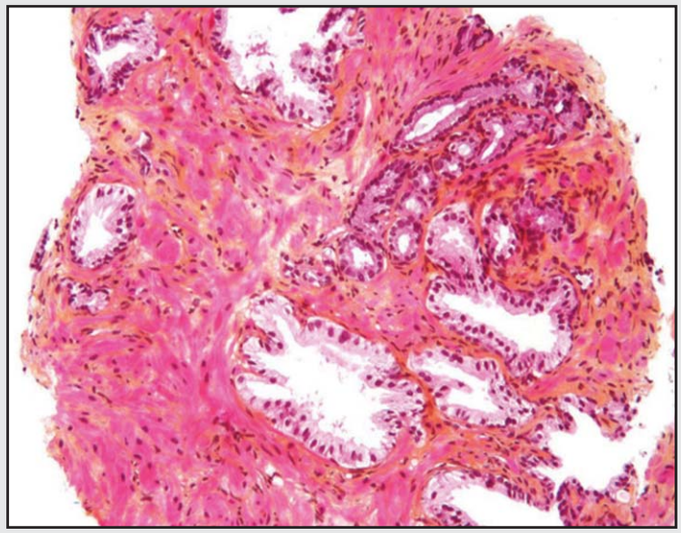


*Image: Micrograph of normal prostatic glands and those with prostate adenocarcinoma (upper right portion of image) (Photo courtesy of Wikimedia Commons).*

# Barth Syndrome Stem Cells Reveal Details of a Rare Heart Defect

Skin cells taken from Barth syndrome patients were used to generate stem cells that differentiated into defective heart tissue in culture.

Barth syndrome (type II 3-Methylglutaconic aciduria) is caused by mutation of the tafazzin gene. Tafazzin is responsible for remodeling of a phospholipid cardiolipin (CL), the signature lipid of the mitochondrial inner membrane. As a result, Barth syndrome patients exhibit defects in CL metabolism, including aberrant CL fatty acyl composition, accumulation of monolysocardiolipin (MLCL), and reduced total CL levels. About 120 cases of Barth syndrome, which is found exclusively in males, have been documented to date, but the syndrome is believed to be severely under-diagnosed and has been estimated to occur in one out of approximately 300,000 births.

Investigators at Harvard University (Cambridge, MA, USA; www.harvard.edu) obtained skin cells from two Barth syndrome patients. The skin cells were induced to become stem cells carrying the patients' TAZ mutations. The stem cells were cultured on chips lined with human extracellular matrix (ECM) proteins that mimicked their natural environment. Under these conditions the stem cells matured into a conglomerate of cardiomyocytes that mimicked heart tissue. Due to the presence of the TAZ mutations the heart tissue demonstrated very weak contractions, similar to a diseased human heart.

The investigators used this novel model system to define metabolic, structural, and functional abnormalities associated with TAZ mutation. They found that excess levels of reactive oxygen species (ROS) mechanistically linked TAZ mutation to impaired cardiomyocyte function. In addition, they used a gene therapy technique to provide the normal TAZ protein to the diseased tissue. Results published in the May 11, 2014, online edition of the journal *Nature Medicine* showed that inducing TAZ mutation in normal cardiomyocytes weakened contractions while addition of normal TAZ to the Barth syndrome cardiomyocytes corrected the contractile defect.

"The TAZ mutation makes Barth syndrome cells produce an excess amount of reactive oxygen species, or ROS – a normal byproduct of cellular metabolism released by mitochondria – which had not been recognized as an important part of this disease," said senior author Dr. William Pu, associate professor of cardiology at Harvard University. "We showed that, at least in the laboratory, if you quench the excessive ROS production then you can restore contractile function. "Now, whether that can be achieved in an animal model or a patient is a different story, but if that could be done, it would suggest a new therapeutic angle."

# A Pair of Gene Splice Isoforms Has Opposite Effects on Cancer Development

Two distinct splice isoforms of the MAP kinase interacting serine/threonine kinase 2 (MKNK2) gene have dramatically different roles in cancer development and growth.

It is known that the protein products of MKNK2 phosphorylate the eukaryotic initiation factor 4E (eIF4E), thus playing important roles in the initiation of mRNA translation, oncogenic transformation, and malignant cell proliferation. However, it has come to light that MKNK2 is alternatively spliced with the two splicing isoforms having different last exons: Mnk2a, which contains a MAPK-binding domain, and Mnk2b, which lacks it.

Investigators at the Hebrew University of Jerusalem (Israel; www.huji.ac.il) reported in the April 10, 2014, online edition of the journal *Cell Reports* that the Mnk2a isoform was a tumor suppressor that was downregulated in human cancers. This isoform interacted with, phosphorylated, and activated p38-MAPK, leading to activation of its target genes and to p38alpha-mediated cell death. Thus, Mnk2a downregulation by alternative splicing was a tumor suppressor mechanism that was lost in some breast, lung, and colon tumors.

On the other hand, the Mnk2b isoform was found to be pro-oncogenic and did not activate p38-MAPK, while still enhancing eIF4E phosphorylation.

These results suggested that Mnk2 alternative splicing served as a switch in several cancers to downregulate a tumor suppressor isoform (Mnk2a) that activates the p38-MAPK stress pathway and to induce an isoform (Mnk2b) that does not activate this pathway and is pro-oncogenic.

"The mechanism we discovered explains how cancer cells eliminate the anticancer form of Mnk2 without changing their DNA, and how they become resistant to anticancer treatments – a problem which exists for almost every cancer treatment today," said senior author Dr. Rotem Karni, senior lecturer of biochemistry and molecular biology at the Hebrew University of Jerusalem.

# Loss of Ron Signaling Linked to Development of Inflammatory Bowel Disease

Cancer researchers have found that decreased molecular signaling by the Ron receptor tyrosine kinase (macrophage-stimulating protein receptor) is linked to the development of inflammatory bowel disease (IBD), a group of chronic inflammatory disorders of the intestine that result in painful and debilitating complications. The Ron receptor tyrosine kinase, a member of the MET proto-oncogene family, is a pathogenic factor implicated in tumor malignancy. Specifically, aberrations in Ron signaling result in increased cancer cell growth, survival, invasion, angiogenesis, and drug resistance. Biochemical events such as ligand binding, receptor overexpression, generation of structure-defected variants, and point mutations in the kinase domain contribute to Ron signaling activation.

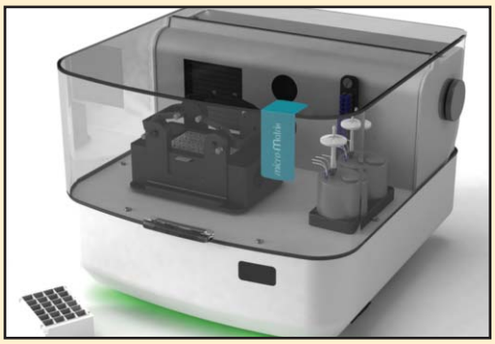
Investigators at the University of Cincinnati (Ohio, USA; www.uc.edu) have now found that decreased Ron signaling is linked to the development of IBD. This data was obtained from experiments conducted with a line of mice that had been genetically engineered to lack the tyrosine kinase signaling domain of Ron (TK-/- mice). These animals and wild-type controls were utilized as a well-characterized model of chronic colitis induced by cyclic exposure to dextran sulfate sodium.

Results reported in the April 17, 2014, online edition of the *American Journal of Physiology-Gastrointestinal and Liver Physiology* revealed that TK-/- mice were more susceptible to injury as judged by increased mortality compared to control mice and developed more severe colitis. In addition, loss of Ron led to significantly reduced body weights and more aggressive clinical histopathologies. Ron loss also resulted in a dramatic reduction in colonic epithelial cell proliferation and increased proinflammatory cytokine production, which was associated with alterations in important signaling pathways known to regulate IBD.

"Genome-wide linkage studies have identified the Ron receptor tyrosine kinase and its hepatocyte growth factor-like protein (HGFL) as genes highly associated with IBD," said senior author Dr. Susan Waltz, professor in of cancer biology at the University of Cincinnati. "However, only scant information exists on the role of Ron or HGFL in IBD. Based on the linkage of Ron to IBD, we examined the biological role of Ron in colitis."

"We found that genetic loss of Ron led to aggressive inflammation and damage to the colon of models with IBD," said Dr. Waltz. "In addition, there are a number of small changes called single nucleotide polymorphisms (SNP) in humans which map to both the Ron and HGFL gene and have been identified to strongly associate IBD disease in humans. Our studies suggest that these SNPs may reduce the function of Ron and HGFL leading to chronic intestinal inflammation and damage. With the knowledge that we have gained in studying these proteins in cancer biology, we hope this information may be translated to help patients with Crohn's disease and ulcerative colitis. Further studies on the Ron signaling pathway are needed and could reveal an important new target for these conditions."

*Image: Researcher Susan Waltz, PhD, and scientists in her lab have done what is believed to be the first direct genetic study to document the important function for the Ron receptor, a cell surface protein often found in certain cancers, and its genetic growth factor, responsible for stimulating cell growth, in the development and progression of IBD (Photo courtesy of Cincinnati Cancer Center / University of Cincinnati Cancer Institute).*



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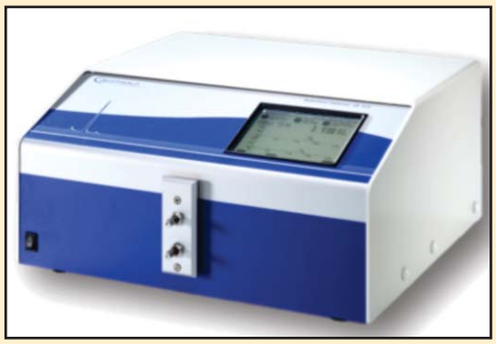

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## Next-Generation Bio-Safety Cabinet Provides Flexible Animal Handling Solutions

Biotech and other life science laboratories that work with animals will benefit from a new line of next-generation biological safety cabinets.

The new LabGard ES NU-677 Animal Class II, Type A2 Animal Handling Biological Safety Cabinet and Cage Changing Station is manufactured and marketed by NuAire (Plymouth, MN, USA; www.nuaire.com), an industry leader in laboratory equipment manufacturing for more than 40 years.

The NU-677 is remarkably flexible, being both mobile and height adjustable. These features help to reduce strains that develop from repeated movements in the arm, neck, and shoulder of laboratory workers. A pre-filter built into the back wall of the cabinet extends the working life of the HEPA filters by trapping animal hair and dander. Thus, the cabinet can handle a 300% increase in filter loading without a significant reduction in air delivery. The technician is protected from airborne contaminants by an aerodynamic air foil that returns air into the front grill. The advanced motor system reduces operating costs by 40%, as it generates less heat and reduces stress while operating at lower decibel levels.

The NU-677 has been certified by the National Sanitation Foundation (Ann Arbor, MI, USA; www.nsf.org) according to ANSI 49. The National Sanitation Foundation was founded in 1944 with the mission to protect and improve global human health. As an independent, accredited organization, it develops standards and tests and certifies products and systems. In addition, it provides auditing, education, and risk management solutions for public health and the environment. The National Sanitation Foundation certifies the design, construction, and performance of bio-safety cabinets to NSF/ANSI Standard 49 and runs the Bio-safety Cabinet Field Certifier Accreditation Program.

*Image: The LabGard model NU-677 animal handling biological safety cabinet (Photo courtesy of NuAire).*

## AFM-Enabled Scanning Electrochemical Microscopy Launched

A new atomic force microscopy (AFM)-enabled Scanning Electrochemical Microscopy (SECM) mode includes an integrated technology package that enables scientists to perform scanning electrochemical microscopy on conductive and insulating samples.

The system uses an Agilent (Santa Clara, CA, USA; www.agilent.com) atomic force microscope, which can be used in a timesaving manner, with nanoscale resolution. Agilent designed the SECM mode to deliver both good performance and ease of use. Hours of setup time are eliminated, so data can be collected immediately.

The new SECM mode provides great utility for a broad range of applications. These include investigations of homogeneous and heterogeneous electron transfer reactions, imaging of biologically active processes, surface modification, analysis of thin films (e.g., pinhole detection, conformality), screening of catalytic material (e.g., fuel cell catalysts), and studies of corrosion processes.

At the technological core of Agilent's SECM mode is the novel EC SmartCart, an easy-to-handle cartridge that combines a nanoelectrode with a premounted AFM tip. EC SmartCart probes come pretested and ready-to-scan for Agilent atomic force microscopes. A customized nose cone for the scanner accepts the cartridge.

Produced via microfabrication techniques, the bifunctional probes ensure a constant and controlled distance between the tip-integrated electrode and the sample surface, significantly improving performance. Agilent's EC SmartCart probes enable high-resolution topographical imaging while simultaneously mapping electrochemical information via the AFM probe-integrated electrode.

The probes provide scientists with inherently synchronized structure-activity information. SECM mode also offers scientists industry-leading in situ research capabilities. An environmental chamber and special sample plates designed specifically for EC applications, as well as a new dual-chamber glove box that fits within an acoustic isolation chamber, enhance experimental control. In addition, a built-in potentiostat affords scientists a series of different sensitivity settings covering four orders of magnitude of currents. Full-featured Agilent PicoView software further extends experimental flexibility and control plus functions for Chronoamperometry and Differential Pulse Voltammetry experiments, among others. Agilent's new SECM mode can improve the vision of electrochemistry science at the nanoscale.

An environmental chamber and special sample plates designed specifically for EC applications, as well as a new dual-chamber glove box that fits within an acoustic isolation chamber, enhance experimental control. In addition, a built-in potentiostat affords scientists a series of different sensitivity settings covering four orders of magnitude of currents.

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The ISOLUTE SLE+ 48-well microplates are designed to enable extraction of larger sample volumes (1 mL total load volume). The plates are ideal for extraction of small molecule drugs, metabolites, and endogenous biomarkers from biological fluid samples prior to LC-MS/MS and GC-MS.

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**BioTek Instruments**

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The ZEISS Smartzoom 5 features an optical engine that combines three functions in a single component: zoom, overview camera, and coaxial illumination. The system is ideal for QC/QA applications, delivering repeatable results, enhanced images, and easy documentation.

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## Electronic Pipetting System Boasts Adjustable Tip Distances

A recently introduced electronic pipetting system – now available for biotech and life science researchers – boasts the ability to adjust the distance between tips while maintaining precise sample volumes on every channel.

The Thermo Fisher Scientific (Milford, MA, USA; www.thermofisher.com) E1-ClipTip electronic pipettes combine the security of the proprietary "Cliptip" tip locking mechanism with the freedom of adjustable tip spacing.

Cliptip enables secure tip attachment with low tip attachment and ejection forces. The system guarantees an airtight seal on every channel, which ensures consistent and accurate liquid transfer for higher quality results. Adjustable tip spacing allows users to transfer multiple samples between different labware formats using one pipette, resulting in fewer repetitions and 90% less time compared to single channel manual pipettes.

"Scientists working in liquid handling and sample preparation need pipettes they can trust," said Raymond Mercier, business director, liquid transfer at Thermo Fisher Scientific. "The Thermo Scientific E1-ClipTip electronic pipette's interlocking technology provides outstanding sample security and makes pipetting more efficient with the ability to transfer samples quickly between different labware formats using the same pipette throughout the protocol."

*Image: The E1 ClipTip multichannel pipette (Photo courtesy of Thermo Fisher Scientific).*

## Brain Buffer System Overcomes Molecular Disturbances in Circadian Clock

New evidence has been found for neuronal network communication that helps create a behavioral buffer in the brain to overcome certain disturbances in the molecular level circadian clock rhythms.

Circadian clocks time the sleep/wake cycles as well as many other physiological and cellular pathways to daily 24 hour rhythms. In *Drosophila*, CLOCK (CLK) and CYCLE (CYC) proteins initiate the circadian system by promoting rhythmic transcription of hundreds of genes. Abolishment of circadian transcriptional oscillations (CTOs) has been shown to abolish circadian function. However, previous studies used manipulations in which the abolishment of the CTOs was very dramatic and involved strong up- or down-regulation of circadian genes.

In this study, a research team led by Sebastian Kadener, assistant professor at the Hebrew University of Jerusalem (Israel; www.huji.ac.il), used an innovative genetic approach that enabled them to generate *Drosophila melanogaster* fruit flies in which the amplitude of CLK-driven CTOs was reduced in a controlled way, either partially (approx. 60%) or strongly (90%). To the best of their knowledge, this is the first time CTOs have been partially damped in a living organism and their role assessed comprehensively.

The researchers postulated that in the brain, communication among the circadian neuronal groups can compensate for the dampened CTOs. This is not surprising, as results from studies on locomotor activity patterns in mammals with core clock protein mutations are among the same lines. However, in mammals the molecular machinery that drives circadian rhythms in the central versus the peripheral oscillators differs, whereas this does not seem to be the case in flies. Yet, in this study, the partial decrease in the amplitude of CTOs led to impaired function of circadian outputs in peripheral functions but did not significantly affect circadian locomotor behavior. This suggests that the clock in the brain has a specific compensatory mechanism. Moreover, flies with reduced CTOs that also had impaired circadian neuronal communication displayed aberrant circadian behavior rhythms.

The partially reduced CTOs led to low amplitude circadian protein oscillations (CPOs) that were not sufficient to drive outputs of peripheral oscillators, while circadian rhythms in locomotor activity were resistant to these partial reductions. This resilience of the brain oscillator was found to depend on communication among circadian neurons in the brain. Indeed, the capacity of the brain oscillator to overcome the low amplitude CTOs depends on the action of the neuropeptide PDF and on the pdf-expressing cells having equal or higher amplitude of CTOs than the rest of the circadian neuronal groups in the brain.

These findings support the idea of network buffering mechanisms that allows the brain to drive robust behavioral circadian rhythms even with low amplitude molecular oscillations. Therefore, in addition to revealing the importance of high amplitude CTOs for cell-autonomous circadian timekeeping, this work demonstrates that the brain's circadian neuronal network has an essential system that protects against disturbances in circadian transcription in the brain.

The study, by Weiss R. et al., was described in the journal *PLOS Genetics*, published April 3, 2014.

# Nanodelivery System Securely Targets Cancer Cells

Scientists have devised a tunable virus that works similar to a safe deposit box. It takes two keys to open it and release its therapeutic payload.

The Rice University (Houston, TX, USA; www.rice.edu) laboratory of bioengineer Dr. Junghae Suh has developed an adeno-associated virus (AAV) that unlocks only in the presence of two selected proteases, enzymes that cut up other proteins for disposal. Because specific proteases are elevated at tumor sites, the viruses can be designed to target and destroy the cancer cells.

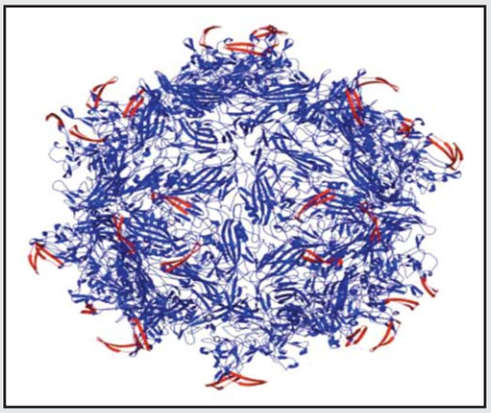
The research was published online May 5, 2014, in the American Chemical Society (ACS) journal *ACS Nano*. AAVs are comparatively benign and have been intensely studied as delivery vehicles for gene therapies. Researchers frequently try to target AAVs to cellular receptors that may be somewhat overexpressed on diseased cells.

The Rice lab takes a different tactic. "We were looking for other types of biomarkers beyond cellular receptors present at disease sites," Dr. Suh said. "In breast cancer, for example, it's known the tumor cells oversecrete extracellular proteases, but perhaps more important are the infiltrating immune cells that migrate into the tumor microenvironment and start dumping out a whole bunch of proteases as well. So that's what we're going after to do targeted delivery. Our basic idea is to create viruses that, in the locked configuration, can't do anything. They're inert," she said. When programmed AAVs encounter the right protease keys at sites of disease, "these viruses unlock, bind to the cells and deliver payloads that will either kill the cells for cancer therapy or deliver genes that can fix them for other disease applications."

Dr. Suh's lab genetically inserts peptides into the self-assembling AAVs to lock the capsids, the hard shells that protect genes positioned within. The target proteases spot the peptides "and chew off the locks," effectively unlocking the virus and allowing it to attach to the diseased cells. "If we were just looking for one protease, it might be at the cancer site, but it could also be somewhere else in your body where you have inflammation. This could lead to undesirable side effects," she said. "By requiring two different proteases – let's say protease A and protease B – to open the locked virus, we may achieve higher delivery specificity since the chance of having both proteases elevated at a site becomes smaller."

Molecular-imaging techniques in the future will be used to detect both the identity and concentration of elevated proteases. "With that information, we would be able to pick a virus device from our panel of engineered variants that has the right properties to target that disease site. That's where we want to go," Dr. Suh said.

Dr. Suh reported that elevated proteases are found around many diseased tissues. She suggested these protease-activatable viruses may be useful for the treatment of not only cancers but also neurologic diseases, such as stroke, Parkinson's and Alzheimer's diseases, and heart diseases, including myocardial infarction and congestive heart failure.



The eventual outcome of this technology is to design viruses that can carry out a combination of steps for targeting. "To increase the specificity of virus unlocking, you can imagine creating viruses that require many more keys to open," Dr. Suh stated. "For example, you may need both proteases A and B as well as a cellular receptor to unlock the virus. The work reported here is a good first step toward this goal."

*Image: An adeno-associated virus capsid (blue) modified by peptides (red) inserted to lock the virus is the result of research into a new way to target cancerous and other diseased cells. The peptides are keyed to proteases overexpressed at the site of diseased tissues; they unlock the capsid and allow it to deliver its therapeutic cargo (Photo courtesy of Junghae Suh / Rice University).*

# Molecules Engineered to Fight Alzheimer's And Other Neurodegenerative Disorders

Researchers have engineered a set of molecules with the potential to treat most neurodegenerative diseases that are characterized by misfolded proteins, such as Alzheimer's, Parkinson's, and Huntington's diseases. These molecules are based on what NeuroPhage Pharmaceuticals, Inc. (Cambridge, MA, USA; www.neurophage.com), the developer of the technology, calls a general amyloid interaction motif (GAIM), which recognizes a characteristic that is typical to many toxic, misfolded proteins, not only one type of misfolded protein. This approach provides a range of therapeutic targets, so that a number of pathologies, such as amyloid beta plaques, tau tangles and alpha-synuclein Lewy bodies, can all be tackled simultaneously with a single drug candidate.

Moreover, GAIM molecules have been shown to not only prevent the formation of new toxic protein aggregates but can also dissipate existing aggregates in the form of both soluble oligomers and insoluble fibers, such as plaques and tangles.

"The research published [...] describes GAIM, NeuroPhage's unique approach to treat diseases characterized by misfolded proteins. GAIM has the potential to provide a more robust response than previous therapies because it enables the simultaneous targeting of multiple pathologies within a single disease," said Dr. Richard Fisher, chief scientific officer at NeuroPhage. The findings of this technology were published online April 22, 2014, in the *Journal of Molecular Biology*.

Researchers used a range of techniques, including X-ray fiber diffraction and nuclear magnetic resonance spectroscopy (NMRS), to demonstrate the activities of GAIM. They found that GAIM effectively binds to multiple types of misfolded proteins during their formation in such a way that prevents new toxic protein aggregates from forming. Furthermore, upon incubating GAIM with various misfolded proteins, the researchers observed that GAIM disrupted these assemblies of misfolded proteins by causing a conformational alteration in their structures. This structural change could enable the body's natural disposal processes to recognize and clear the misfolded proteins, which in principle, would enable the brain to return to a more normal state.

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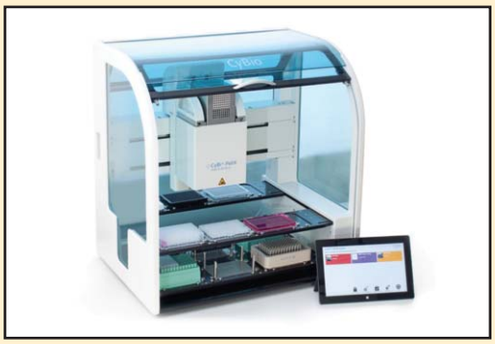

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# RNA Interference Mechanism May Be Used to Treat Cancer

RNA carried by new nanoparticles can silence genes in many organs, and researchers believe that it could be utilized to treat cancer.

RNA interference (RNAi), a technique that can inactivate specific genes inside living cells, holds great potential for treating many disorders caused by malfunctioning genes. However, it has been difficult for scientists to find safe and effective ways to deliver gene-blocking RNA to the correct targets.

Up to now, researchers have received the best results with RNAi targeted to diseases of the liver, partly because it is a normal endpoint for nanoparticles. But now, in a study appearing in the May 11, 2014, issue of the journal *Nature Nanotechnology*, a Massachusetts Institute of Technology (MIT; Cambridge, MA, USA; www.mit.edu)-led team reported achieving the most effective RNAi gene silencing to date in nonliver tissues.

Using nanoparticles designed and screened for endothelial delivery of short strands of RNA called siRNA, the researchers were able to target RNAi to endothelial cells, which form the linings of most organs. This raises the possibility of using RNAi to treat many types of disease, including cancer and cardiovascular disease, according to the researchers.

"There's been a growing amount of excitement about delivery to the liver in particular, but in order to achieve the broad potential of RNAi therapeutics, it's important that we be able to reach other parts of the body as well," remarked Dr. Daniel Anderson, an associate professor of chemical engineering, a member of MIT's Koch Institute for Integrative Cancer Research and Institute for Medical Engineering and Science, and one of the study's senior authors. The article's other senior author is Dr. Robert Langer, a professor at MIT and a member of the Koch Institute.

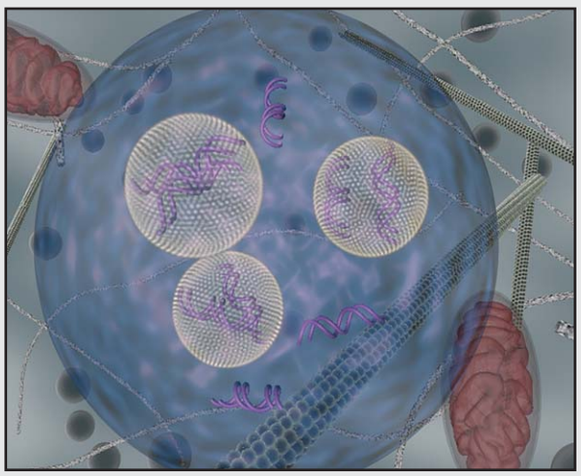
Discovered in 1998, RNAi is a naturally occurring process that allows cells to control their genetic expression. Genetic data are typically carried from DNA in the nucleus to ribosomes, cellular structures where proteins are produced. Short strands of RNA called siRNA attach to the messenger RNA that carries this genetic information, preventing it from reaching the ribosome.

Drs. Anderson and Langer have earlier developed nanoparticles, now in clinical development, that can deliver siRNA to liver cells called hepatocytes by coating the nucleic acids in fatty compounds called lipidoids. Hepatocytes clutch onto these particles because they resemble the fatty droplets that circulate in the blood after a high-fat meal is consumed. "The liver is a natural destination for nanoparticles," Dr. Anderson stated.

Scientists have had some success delivering RNA to nonliver organs, but the MIT scientists wanted to formulate an approach that could achieve RNAi with lower doses of RNA, which could make the treatment more effective and safer.

The new MIT particles consist of three or more concentric spheres made of short chains of a chemically modified polymer. RNA is packaged within each sphere and released once the particles enter a target cell. A major aspect of the MIT system is that the scientists were able to create a "library" of many different substances and rapidly evaluate their potential as delivery agents. They evaluated about 2,400 variants of their particles in cervical cancer cells by measuring whether they could turn off a gene coding for a fluorescent protein that had been added to the cells. They then tested the most promising of those in endothelial cells to see if they could interfere with a gene called TIE2, which is expressed almost exclusively in endothelial cells.

With the best-performing particles, the researchers reduced gene expression by more than 50%, for a dose of only 0.20 mg/kg of solution – about one-hundredth of the amount required with existing endothelial RNAi delivery vehicles. They also showed that they could block up to five genes at once by delivering different RNA sequences.



To demonstrate the potential for treating lung disease, the researchers used the nanoparticles to block two genes that have been implicated in lung cancer – vascular endothelial growth factor (VEGF) receptor 1 and Dll4, which encourage the growth of blood vessels that feed tumors. By blocking these in lung endothelial cells, the researchers were able to slow lung tumor growth in mice and also reduce the spread of metastatic tumors.

Dr. Masanori Aikawa, an associate professor of medicine at Harvard Medical School (Boston, MA, USA; http://hms.harvard.edu), described the new technology as "a monumental contribution" that should help researchers develop new treatments and learn more about diseases of endothelial tissue such as atherosclerosis and diabetic retinopathy, which can cause blindness.

The researchers next plan to explore additional potential targets in hopes that these particles could eventually be deployed to treat cancer, atherosclerosis, and other diseases.

*Image: Lipid nanoparticles (carrying siRNA) are shown as they are transported inside cells using endocytic vesicles (Photo courtesy of Daria Alakhova and Gaurav Sahay).*

# Possible Target for Gene Therapy May Correct Cardiac Hypertrophy

A deficit in the expression of the protein Erbin (ErbB2 interacting protein) has been linked to the development of cardiac hypertrophy and heart failure.

The gene that encodes the Erbin protein is a member of the leucine-rich repeat and PDZ domain (LAP) family. The encoded Erbin protein contains 17 leucine-rich repeats and one PDZ domain. It binds to the unphosphorylated form of the ERBB2 protein and regulates ERBB2 function and localization. Erbin's C-terminal PDZ domain is able to bind to ErbB2, a protein tyrosine kinase, which is often associated with poor prognosis during the development of skin cancer. Its N-terminal region has been shown to affect the Ras signaling pathway by disrupting Ras-Raf interaction.

Investigators at the Hebrew University of Jerusalem (Israel; www.huji.ac.il) looked at Erbin levels in humans and animals with and without cardiac hypertrophy. In addition, they genetically engineered a line of mice to lack the Erbin gene.

They reported in the April 22, 2014, issue of the journal *Proceedings of the National Academy of Sciences of the United States of America (PNAS)* that there was down-regulation of Erbin expression in biopsies derived from human failing hearts.

In mouse models cardiac hypertrophy was induced either by isoproterenol administration or by aortic constriction. In both models the level of Erbin was significantly decreased. The genetically engineered Erbin knockout mice rapidly developed decompensated cardiac hypertrophy and following severe pressure overload, all of these mice died from heart failure (compared to only about 30% mortality observed in the control group).

It is known that Erbin inhibited Ras-mediated activation of the extracellular signal-regulated kinase (ERK) by binding to the protein Soc-2 suppressor of clear homolog (Shoc2). The data obtained during this study showed that ERK phosphorylation was enhanced in the heart tissues of the Erbin knockout mice. Furthermore, Erbin associated with Shoc2 in both whole hearts and in cardiomyocytes, and that in the absence of Erbin, Raf was phosphorylated and bound to Shoc2, resulting in ERK phosphorylation.

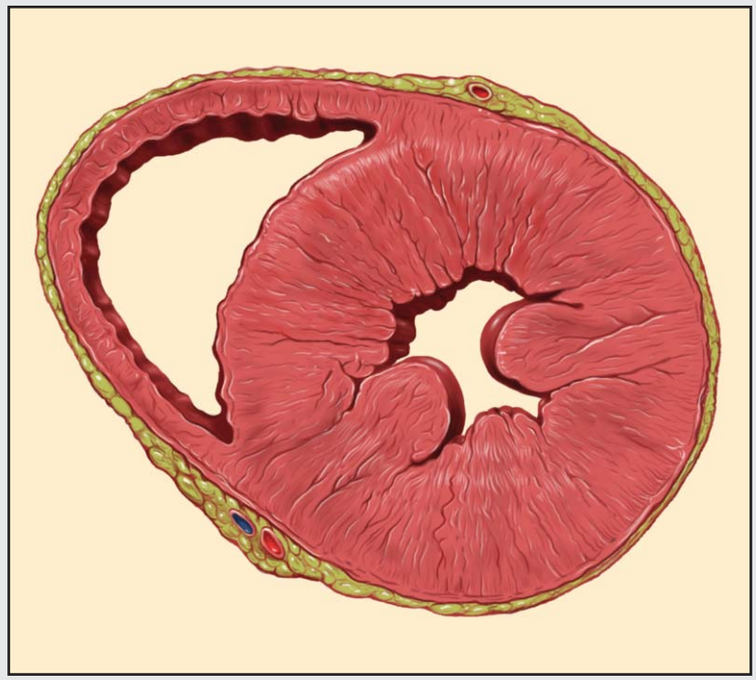


*Image: Left ventricular cardiac hypertrophy in short axis view (Photo courtesy of Patrick Lynch).*

The investigators concluded that, "Erbin is an inhibitor of pathological cardiac hypertrophy, and this inhibition is mediated, at least in part, by modulating ERK signaling. We describe a cardioprotective role for Erbin, which suggests it is a potential target for cardiac gene therapy."

# Bioinformatics Application Designed to Look for New Uses for Old Drug

By tying together cancer gene expression patterns with drug activity, scientists have found a possible cancer therapy concealed within an antimicrobial agent.

Developing and evaluating a new anticancer drug can cost a huge amount of money and take many years of research. Finding an effective anticancer medication from the pool of drugs already approved for the treatment of other medical disorders could slash a substantial amount of time and money from the process.

Now, using a cutting-edge bioinformatics approach, a team led by investigators from Beth Israel Deaconess Medical Center (BIDMC; Boston, MA, USA; www.bidmc.org) has found that the approved antimicrobial drug pentamidine may help in the treatment of patients with advanced kidney cancer. Described online May 1, 2014, in the journal *Molecular Cancer Therapeutics*, these new findings reveal how connecting cancer gene expression patterns with drug activity might help advance cancer care.

"The strategy of repurposing drugs that are currently being used for other indications is of significant interest to the medical community as well as the pharmaceutical and biotech industries," said senior author Towia Libermann, PhD, director of the Genomics, Proteomics, Bioinformatics and Systems Biology Center at BIDMC and associate professor of medicine at Harvard Medical School (Boston, MA, USA). "Our results demonstrate that bioinformatics approaches involving the analysis and matching of cancer and drug gene signatures can indeed help us identify new candidate cancer therapeutics."

Renal cell cancer consists of multiple subtypes that are likely caused by different genetic mutations. Over the years, Dr. Libermann has been working to identify new disease markers and therapeutic targets through gene expression signatures of renal cell cancer that distinguish these diverse cancer subtypes from each other, as well as from healthy individuals. In this new study, he and his colleagues were searching for agents that might be effective against clear cell renal cancer, the most common and highly malignant subtype of kidney cancer. Even though patients with early stage disease can frequently be effectively treated through surgery, up to 30% of patients with renal cell cancer present with advanced stages of disease at the time of their diagnosis.

To pursue this search, the investigators are using the Connectivity Map (C-MAP) database (www.broadinstitute.org/cmap), a compendium of gene expression data from human cancer cells treated with hundreds of small molecule drugs. "C-MAP uses pattern-matching algorithms to enable investigators to make connections between drugs, genes and diseases through common, but inverse, changes in gene expression," stated Dr. Libermann. "It provided us with an exciting opportunity to use our renal cell cancer gene signatures and a new bioinformatics strategy to match kidney cancer gene expression profiles from individual patients with gene expression changes inducted by various commonly used drugs."

After identifying drugs that may reverse the gene expression alterations linked with renal cell cancer, the investigators employed assays to measure the effect of the selected drugs on cells. This led to the identification of a small number of US Food and Drug Administration (FDA)-approved drugs that induced cell death in multiple kidney cancer cell lines. The researchers then assessed three of these drugs in an animal model of renal cell cancer and showed that the antimicrobial agent pentamidine (principally used for the treatment of pneumonia) decreased tumor growth and enhanced survival. Gene expression research using microarrays also identified the genes in renal cell cancer that were counteracted by pentamidine.

"One of the main challenges in treating cancer is the identification of the right drug for the right individual," clarified first author Luiz Fernando Zerbini, PhD, of the International Center for Genetic Engineering and Biotechnology (Cape Town, South Africa), adding that this bioinformatics application could be an especially valuable lower-cost model in developing countries.

The authors reported that their next phase of the research will be to assess the potential of pentamidine used in combination with the existing standard-of-care therapies to treat kidney cancer. "Since the drugs we are evaluating are already FDA-approved, successful studies in preclinical animal models may enable us to rapidly move these drugs into clinical trials," added Dr. Libermann.

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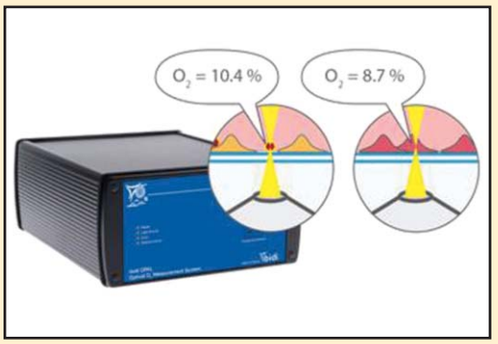


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# Metallopolymers Protect Penicillin-Like Antibiotics from Bacterial Beta-Lactamase

Novel drug combinations that unite classical penicillin-like antibiotics with metallopolymers effectively kill bacteria, including "superbugs" such as MRSA (methicillin-resistant *Staphylococcus aureus*) that had developed beta-lactamase enzyme-based resistance to the antibiotics.

Metallopolymers are a class of polymers with metal atoms either in the backbone or at the side chain. These polymers exhibit many unprecedented properties and functions that conventional organic polymers usually lack. Among metallopolymers, metallocene-containing polymers have attracted significant attention due to their unique electrochemical, catalytic, and optical properties. Metallocene-containing polymers are widely used for redox active systems as recognition of ions and sugars and modification of electrodes.

MRSA, a complex of multi-drug-resistant Gram-positive bacterial strains, has proven especially problematic in both hospital and community settings by deactivating conventional beta-lactam antibiotics, including penicillins, cephalosporins, and carbapenems, through various mechanisms, resulting in increased mortality rates and hospitalization costs.

To correct this problem, investigators at the University of South Carolina (Columbia, USA; www.sc.edu) developed an improved class of beta-lactam antibiotics by conjugating classical penicillin-like antibiotics to cobaltocenium metallopolymers.

They reported in the March 17, 2014, online edition of the *Journal of the American Chemical Society* that these combinations exhibited a synergistic effect against MRSA by efficiently inhibiting activity of beta-lactamase and effectively lysing bacterial cells. Various conventional beta-lactam antibiotics, including penicillin-G, amoxicillin, ampicillin, and cefazolin, were protected from beta-lactamase hydrolysis via the formation of unique ion-pairs between their carboxylate anions and cationic cobaltocenium moieties.

"Instead of developing new antibiotics, here we ask the question, "Can we recycle the old antibiotics?" With traditional antibiotics like penicillin G, amoxicillin, ampicillin, and so on, can we give them new life?" In the United States every year, around 100,000 patients die of bacteria-induced infections," said senior author Dr. Chuanbing Tang, professor of chemistry and biochemistry at the University of South Carolina. "And the problem is increasing because bacteria are building resistance. It is a really, really big problem, not only for individual patients, but also for society."

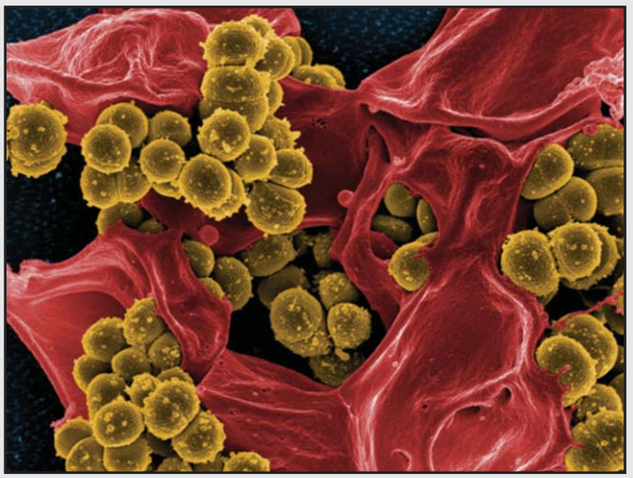


*Image: The MRSA superbug (in yellow), often found in hospitals, is resistant to antibiotics and can lead to death, but a new polymer-antibiotic combo to deal with MRSA is in the works (Photo courtesy of the National Institute of Allergy and Infectious Diseases).*

# Melanoma Development Depends on the Activity of the RUNX2 Transcription Factor

The transcription factor RUNX2 (runt-related transcription factor 2) has been found to play a critical role in melanomagenesis, the processes leading to development of the skin cancer, melanoma.

The RUNX2 gene is a member of the RUNX family of transcription factors and encodes a nuclear protein with a Runt DNA-binding domain. This protein is essential for osteoblastic differentiation and skeletal morphogenesis and acts as a scaffold for nucleic acids and regulatory factors involved in skeletal gene expression.

Investigators at the Rutgers Cancer Institute (New Brunswick, NJ, USA; www.cinj.org) examined the role of the RUNX2 transcription factor in melanomagenesis. They reported in the March 31, 2014, online edition of the journal *Cancer Letters* that the expression of transcriptionally active RUNX2 was increased in melanoma cell lines as compared with normal human melanocytes. Using a melanoma tissue microarray, they showed that RUNX2 levels were higher in melanoma cells as compared with nevic melanocytes.

Genetic silencing of RUNX2 in melanoma cell lines significantly decreased Focal Adhesion Kinase expression and inhibited cell growth, migration, and invasion ability. Furthermore, the pro-hormone cholecalciferol reduced RUNX2 transcriptional activity and decreased migration of melanoma cells, further suggesting a role of RUNX2 in melanoma cell migration.

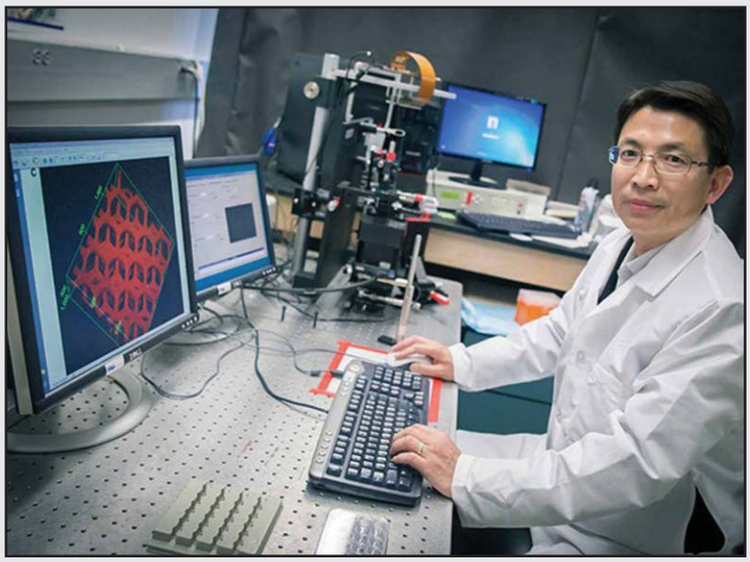
"Successful efforts to render transcription factors "drugable" by interfering with different aspects of their transcriptional activity make this class of proteins attractive targets for therapy," said senior author Dr. Karine Cohen-Solal, assistant professor of medicine at the Rutgers Cancer Institute. "Exploring the role of RUNX2 in the development of melanoma is likely to reveal new mechanisms driving melanoma progression and identify a target for novel antimelanoma agents, thereby opening new avenues for the treatment of this disease."

# Bioprinting 3D Technology Mimics Liver to Detoxify Blood

Nanoengineers have developed a three-dimensional (3D)-printed device to act like the liver to remove harmful toxins from the blood. The device, which is designed to be used outside the body, similar to dialysis, utilizes nanoparticles to trap pore-forming toxins that can injure cellular membranes and are a major factor in disorders that result from stings, animal bites, and bacterial infections.

The study's findings were published May 8, 2014, in the journal *Nature Communications*. Nanoparticles have already been shown to be effective at neutralizing pore-forming toxins in the blood, but if those nanoparticles cannot be effectively digested, they can accumulate in the liver creating a risk of secondary poisoning, particularly among patients who are already at risk of liver failure. To resolve this problem, a team of investigators, led by University of California, San Diego's (UCSD; USA; www.ucsd.edu) nanoengineering Prof. Shaochen Chen devised a 3D-printed hydrogel matrix to hold nanoparticles, forming a device that mimics the function of the liver by sensing, attracting, and capturing toxins channeled from the blood.

The device, which is in the proof-of-concept phase, replicates the structure of the liver but has a larger surface area designed to effectively lure and trap toxins within the device. In an in vitro study, the device totally neutralized pore-forming toxins. "One unique feature of this device is that it turns red when the toxins are captured," said the co-first author, Xin Qu, who is a postdoctoral researcher working in Prof. Chen's laboratory. "The concept of using 3D printing to encapsulate functional nanoparticles in a biocompatible hydrogel is novel," said Prof. Chen. "This will inspire many new designs for detoxification techniques since 3D printing allows user-specific or site-specific manufacturing of highly functional products."



Prof. Chen's lab has already validated the ability to print complex 3D microstructures, such as blood vessels, in only seconds out of soft biocompatible hydrogels that contain living cells.

*Image: A team led by nanoengineering professor Shaochen Chen has developed a 3D device that, like a human liver, removes toxins from the bloodstream (Photo courtesy of UCSD).*

# Canada to Establish "Big Data" Cloud-Computing Facility for Cancer Research

The Government of Canada announced CAD 7.3 million in funding for a collaboration – both in Canada and internationally – to develop tools that can effectively manipulate huge amounts of data to help find cures for cancer.

Recently developed technologies for genetic analysis have created almost unimaginable amounts of data, measured in petabytes. Genomic researchers are eager to analyze these data and identify genetic clues that could point to new ways to prevent or cure cancer. Such an effort, however, requires thousands of high-performance computers working in tandem, along with the yet-unavailable software tools that can coordinate such an intimidating and complex task.

Funded through Canada's Natural Sciences and Engineering Research Council of Canada's (NSERC; Ottawa, ON, Canada; www.nserc-crsng.gc.ca) Discovery Frontiers, the new project will develop effective new computing tools, so that researchers can study genetic data from thousands of cancers to learn more about how tumors develop, and which treatments work best.

At the center of the project will be a new cloud-computing facility, the Cancer Genome Collaboratory (Ottawa, ON, Canada), capable of processing genetic profiles gathered by the International Cancer Genome Consortium (ICGC; www.icgc.org) from tumors in some 25,000 patients worldwide. The powerful new data-mining tools are expected to be available in 2015 for beta testing by selected cancer genomics and privacy researchers. The facility is planned to be opened to the wider research community in 2016. Researchers will be able to formulate questions about cancer risk, tumor growth, and drug treatments, and extract an analysis against the data.

The NSERC initiated the project with a partnership among federal granting organizations that also include Genome Canada, the Canada Foundation for Innovation (CFI), and the Canadian Institutes of Health Research (CIHR).

The University of Chicago (IL, USA) is also providing critical computing resources for the project. Furthermore, a large initial donation of genomic data will come from the International Cancer Genome Consortium, and brings together researchers from some 16 jurisdictions worldwide. The International Cancer Genome Consortium is the largest worldwide coordinated effort to produce a catalog of genetic structure of cancer organisms. Its 10-year goal is to characterize the genetic materials from tumors in 500 patients for each of the major cancer types.

"Canada and many other nations around the world have already invested tremendous resources in sequencing of thousands of cancer genomes, but until now there has been no viable long-term plan for storing the raw sequencing data in a form that can be easily accessed by the research community. The Cancer Genome 'Collaboratory' will open this incredibly important data set to researchers from laboratories large and small, enabling them to achieve new insights into the causes of cancer and to develop innovative new ways to diagnose and manage the disease," noted Lincoln Stein, director, Informatics and Biocomputing Program, Ontario Institute for Cancer Research, and professor, department of molecular genetics, University of Toronto (Canada).

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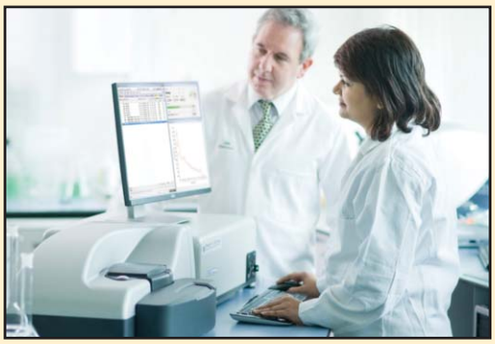

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The Zetasizer Helix is designed to enable the detailed study of mechanisms or protein aggregation. The system combines DLS technology with Raman spectroscopy, and allows the accurate measurement of protein size and structure from a single small volume sample.

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**WEIGH MODULES**
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**WELL PLATE SHAKER**
**MO BIO Laboratories**
The 96-well plate shaker features an adjustable parameter lock, memory keys for three standard working programs, and automatic centering of plates for easier, quicker, and safer handling. The shaker holds two 96-well plates, and lyses all cell types when used with bead beating.

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# Silly Putty Component Used to Help in Stem Cell Therapies

The sponginess of the setting where human embryonic stem cells are growing, affects the type of specialized cells they will ultimately become, new research shows. Scientists persuaded human embryonic stem cells to convert into working spinal cord cells more effectively by growing the cells on a soft, ultrafine carpet made of a key ingredient in Silly Putty [a substance with unusual properties based on silicone polymers, used as a toy].

The study's findings were published online April 13, 2014, in the journal *Nature Materials*. This research is the first to directly link physical, instead of chemical, signals to human embryonic stem cell differentiation. Differentiation is the process of the source cells morphing into the body's more than 200 cell types that become bone, muscle, nerves, and organs.

Jianping Fu, a University of Michigan (U-M; Ann Arbor, USA; www.umich.edu) assistant professor of mechanical engineering, noted that the findings offer the potential of a more effective way to guide stem cells to differentiate and potentially provide therapies for diseases such as amyotrophic lateral sclerosis (also known as Lou Gehrig's disease), Huntington's, or Alzheimer's.

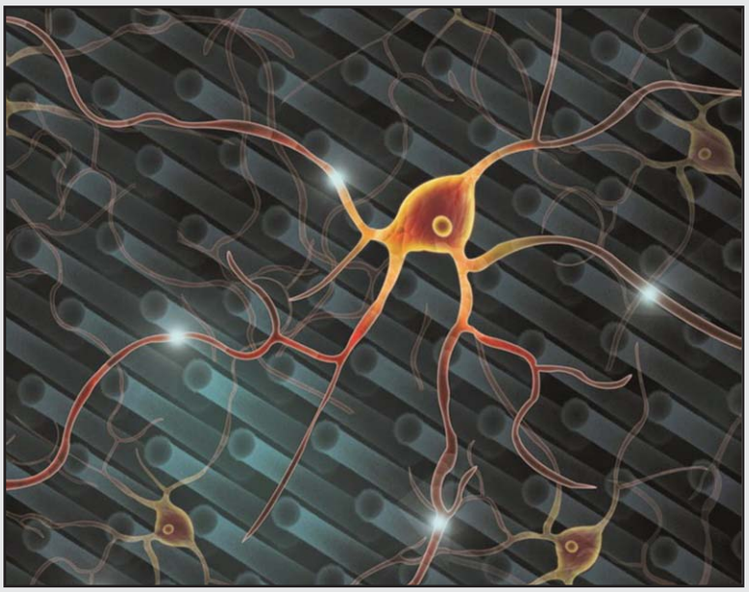
In the specially modified growth system, the "carpets," Prof. Fu and his colleagues designed microscopic posts of the Silly Putty component polydimethylsiloxane to serve as the threads. By varying the post height, the researchers can adjust the stiffness of the surface they grow cells on. Shorter posts are more rigid – similar to an industrial carpet. Taller ones are softer – more plush.

The scientists found that stem cells they grew on the tall, softer micropost carpets turned into nerve cells much faster and more frequently than those they grew on the stiffer surfaces. After 23 days, the colonies of spinal cord cells – motor neurons that regulate how muscles move – that grew on the softer micropost carpets were four times more pure and 10 times larger than those growing on either traditional plates or rigid carpets.

"This is extremely exciting," Prof. Fu said. "To realize promising clinical applications of human embryonic stem cells, we need a better culture system that can reliably produce more target cells that function well. Our approach is a big step in that direction, by using synthetic microengineered surfaces to control mechanical environmental signals."

Prof. Fu is collaborating with physicians at the U-M Medical School. Eva Feldman, a professor of neurology, studies amyotrophic lateral sclerosis (ALS), which paralyzes patients as it kills motor neurons in the brain and spinal cord.

Researchers such as Prof. Feldman believe stem cell therapies – both from embryonic and adult varieties – might help patients grow new nerve cells. The researchers technique to try to generate fresh



neurons from patients' own cells. At this point, they are examining how and whether the process could work, and they hope to try it in humans in the future. "Prof. Fu and colleagues have developed an innovative method of generating high-yield and high-purity motor neurons from stem cells," Prof. Feldman said. "For ALS, discoveries like this provide tools for modeling disease in the laboratory and for developing cell-replacement therapies."

Prof. Fu's findings go deeper than cell counts. The researchers verified that the new motor neurons they obtained on soft micropost carpets showed electrical behaviors comparable to those of neurons in the human body. They also identified a signaling pathway involved in regulating the mechanically sensitive behaviors. A signaling pathway is a route through which proteins ferry chemical messages from the cell's borders to deep inside it. The pathway they narrowed in on, called Hippo/YAP, is also involved in controlling organ size and both causing and preventing tumor growth.

Prof. Fu reported that his findings could also provide clues into how embryonic stem cells differentiate in the body. "Our work suggests that physical signals in the cell environment are important in neural patterning, a process where nerve cells become specialized for their specific functions based on their physical location in the body," he said.

*Image: Researchers cultured stem cells on ultrafine carpets made of microscopic posts of a key ingredient in Silly Putty (Photo courtesy of Ye Tao, Rose Anderson, Yubing Sun, and Jianping Fu / University of Michigan).*

# Novel Apparatus Mimics Human Digestive System for Oral Drug Studies

A team of British drug developers has created an instrument that mimics the human digestive system, which will allow them to accurately determine how orally administered medications are dissolved and then absorbed. Investigators at the University of Huddersfield (United Kingdom; www.hud.ac.uk) sought a way to study the behavior of oral drugs in the digestive tract that would avoid the differences between the digestive systems of humans and laboratory animals.

To this end, they developed an apparatus for testing drug solubility that included a chamber for holding a solvent medium – often a bicarbonate based buffer system – as well as a pH probe connected to tanks of carbon dioxide and helium.

The heart of the apparatus was the control unit that monitored changes in pH of the solvent medium and, as appropriate, fed pH increasing and/or pH reducing gas from the tanks into the chamber. The control unit was able to maintain a uniform pH during testing or could be set to provide a dynamically adjustable pH range, for example to three or more different pH levels in order to test the performance of a drug carrier at different levels of acidity or alkalinity.

"By minimizing human trials we would reduce the cost of development, which is then charged to patients when the drug comes to the market – if the development costs are lower, then we can make new drugs more affordable," said Dr. Hamid Merchant, senior lecturer of pharmaceutics at the University of Huddersfield.

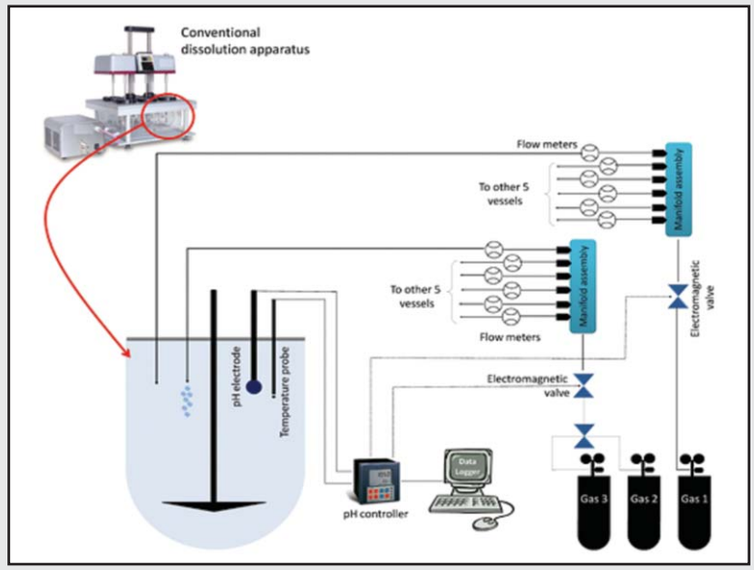



*Image: The testing device includes a chamber for holding a solvent medium plus a pH probe and a control unit. This monitors changes in the pH of the solvent medium in order to test the performance of a drug carrier at different levels of acidity or alkalinity, mimicking the conditions of the gastrointestinal tract. The device is particularly suitable for testing and developing dosage forms for oral delivery of drugs and can also simulate the variability between individuals (Photo courtesy of Dr. Hamid Merchant / University of Huddersfield).*

# Simulation Gives Clues About Forces Underlying Fundamental Cellular Processes

Researchers have developed a simulation model resulting in clues to physical conditions that help drive cell division and motility. The results may also hint at conditions that helped facilitate the original transition from inanimate to living matter.

Active droplets of filamentous material enclosed in a lipid membrane are the main cell-like characteristics modeled in a program, developed by physicists Luca Giomi and Antonio DeSimone of the International School for Advanced Studies (SISSA; Scuola Internazionale Superiore di Studi Avanzati; Trieste, Italy; www.sissa.it), for numerical simulations to investigate the mechanics of "simplified" pre-cell structures. The simulations indicated a spontaneous emergence of features reminiscent of living material – of cell-like motility and division.

The model mimics some of the physical properties of cells: "Our 'cells' are a bare bones representation of a biological cell, which normally contains microtubules, elongated proteins, enclosed in an essentially lipid cell membrane," said Dr. Giomi; "The filaments contained in the 'cytoplasm' of our cells slide over one another exerting a force that we can control." The force exerted by the filaments is the variable that competes with another force, the surface tension that prevents the membrane surrounding the droplet from collapsing. This "competition" generates a flow in the fluid surrounding the droplet, and the droplet is in turn propelled by this self-generated hydrodynamic flow. When the flow becomes very strong, the droplet deforms to the point of dividing: "When the force of the flow prevails over the force that keeps the membrane together we have 'cellular' division," said Dr. DeSimone, director of the SISSA mathLab, SISSA's mathematical modeling and scientific computing laboratory.

The study, described in the April 10, 2014, online issue of the journal *Physical Review Letters*, is a step forward toward creating functional artificial cells and toward a better understanding of the first passages from which life has developed: "Acquiring motility and the ability to divide is a fundamental step for life and, according to our simulations, the laws governing these phenomena could be very simple. Observations like ours can prepare the way for the creation of functioning artificial cells, and not only," said Dr. Giomi. "Our work is also useful for understanding the transition from non-living to living matter on our planet." Chemists and biologists who study the origin of life lack access to cells that are sufficiently simple. "Even the simplest organism existing today has undergone billions of years of evolution, and will always contain fairly complex structures," noted Dr. Giomi.

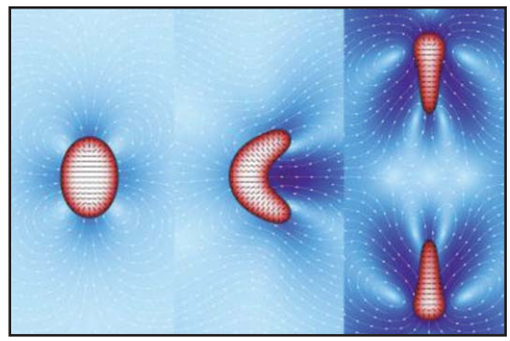


*Image: Cell-like features in computer-simulated active droplets (Photo courtesy of SISSA).*

# Resveratrol Interacts with Estrogen Receptor to Modulate Inflammation

A molecular mechanism has been identified that explains how the wine and grape product resveratrol modulates the inflammatory response by interacting with estrogen receptor-alpha.

Resveratrol (trans-3,5,4'-trihydroxystilbene), a compound found largely in the skins of red grapes, is a component of Ko-jo-kon, a form of oriental medicine used to treat diseases of the blood vessels, heart, and liver. Red wine contains between 0.2 and 5.8 mg/L of resveratrol, depending on the grape variety, while white wine has much less – the reason being that red wine is fermented with the skins, allowing the wine to absorb the resveratrol, whereas white wine is fermented after the skin has been removed. Resveratrol came to scientific attention during the mid-1990s as a possible explanation for the "French Paradox" – the low incidence of heart disease among the French, who eat a relatively high-fat diet. Since then, it has been promoted by manufacturers and examined by scientific researchers as an antioxidant, an anticancer agent, and a phytoestrogen.

Investigators at The Scripps Research Institute (Jupiter, FL, USA; www.scripps.edu) reported in the April 25, 2014, online edition of the journal *eLife* that resveratrol acted as a pathway-selective estrogen receptor-alpha (ERalpha) ligand to modulate the inflammatory response but not cell proliferation. A crystal structure of the ERalpha ligand-binding domain (LBD) as a complex with resveratrol revealed a unique perturbation of the coactivator-binding surface, consistent with an altered coregulator recruitment profile. Gene expression analyses revealed significant overlap of TNFalpha (tumor necrosis factor alpha) genes modulated by resveratrol and estradiol. In addition, the ability of resveratrol to suppress interleukin-6 transcription was shown to require ERalpha and several ERalpha coregulators.

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# Big Data's Direct Coupling Analysis Reveals Clues About Molecular Protease Machines

Researchers have merged genetic and structural data in a Big Data attempt to solve one of the most fascinating mysteries in biology: how proteins perform the regulatory processes in cells upon which all life depends.

The daily life of a motor molecule involves eating and excreting damaged proteins and converting them into harmless peptides ready for disposal. Without these garbage bins, the *Escherichia coli* bacteria they attend to would die. Biophysicists from Rice University (Atlanta, GA, USA; www.rice.edu) used a protease called an FtsH-AAA hexameric peptidase as a model to examine calculations that combine genetic and structural data.

Dr. José Onuchic, a biologic physicist, and postdoctoral researchers Drs. Biman Jana and Faruck Morcos published their new findings March 2014 in the Royal Society of Chemistry journal, *Physical Chemistry Chemical Physics*. The study is the first successful attempt to feed data through their computational technique to describe the complex activity of a large molecular machine formed by proteins. Ultimately, understanding these machines will help researchers design drugs to treat diseases including cancer, the focus of Rice's Center for Theoretical Biological Physics.

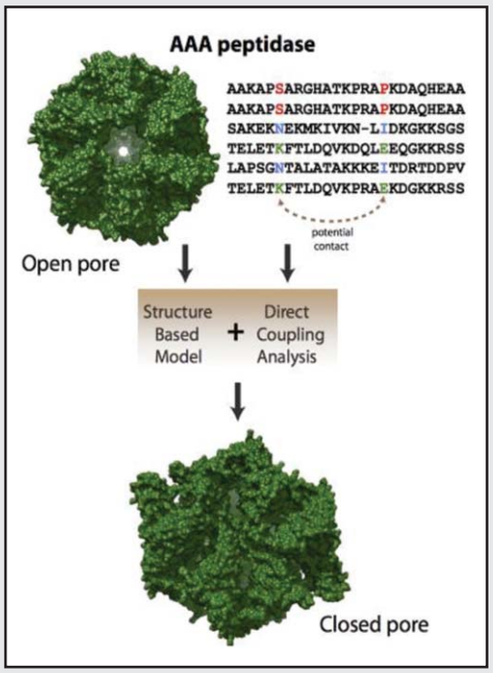
"Structural techniques like X-ray crystallography and nuclear magnetic resonance have worked quite well to help us understand how smaller proteins function," Dr. Onuchic stated. X-rays only take snapshots of constantly moving proteins, he said, "but functional proteins, big protein complexes and molecular machines have multiple conformations. Computational models are also useful, but to understand the full dynamics of these large proteins, where a lot of the interesting biology takes place, we have to supplement them with more information."

That information comes from direct coupling analysis (DCA), a statistical tool developed by Drs. Morcos and Onuchic with colleagues at the University of California, San Diego (UCSD; USA; www.ucsd.edu), and the Pierre and Marie Curie University (Paris, France; www.upmc.fr). DCA looks at the genetic roots of proteins to see how amino acids – the "beads" in the unfolded protein strands – co-evolved to influence the way a protein folds. Each bead carries an inherent energy that contributes to the strand's unique energy topography, which decrees how it folds into its functional state.

Proteins, even after they fold, are in constant motion, acting as catalysts for countless bodily functions. They can combine into larger molecular machines that grab other molecules, "walk" their payloads within a cell or cause muscles to contract. One such biomachine is FtsH (filamentous temperature-sensitive H), a membrane-bound molecule in *E. coli* made of six protein copies that form two connected hexagonal rings. The molecule attracts and degrades misfolded proteins and other cellular waste pulling them in through one ring, which closes similar to a shutter of a camera and traps the proteins. They are sliced apart as they leave through the other ring.

Through molecular simulations using structure-based models and the discovery using DCA of probable couplings in the genetic source of the proteins, the researchers found evidence to support the hypothesis of a "paddling" process in the molecule that Dr. Morcos described as a collapse of the two rings once waste found its way inside. "First the ring pore closes to grab the protein; then the molecule flattens," he said. "Then when the motor is flat, the rings open to release the peptides and the molecule expands again to restart the cycle."

DCA would do little without the deluge of data available since the ability to scan entire genomes became possible, and even routine, in recent years. Recent developments in the 100-year-old skill of crystallography are making better structure-based models available as well. "Even if the mathematical framework was ready and we had crystallographic data for this motor protein in the 1990s, there weren't enough sequences available until the 2000s," Dr. Morcos said. "Now we have all the pieces converging."




Dr. Morcos noted that by better determining essential motor proteins in bacteria will be important as researchers begin to apply DCA to optimize human healthcare. "For us, the most exciting part is that we're now able to tackle really big systems," he said.

*Image: Co-evolved mutations in genetic sequences that code proteins show researchers how a protein is likely to fold and what forms it may take as it carries out its function. Scientists used the technique called direct coupling analysis in combination with structure-based models to find a previously hidden conformation of a molecular motor responsible for degrading misfolded proteins in bacteria (Photo courtesy of Faruck Morcos / Rice University).*

# Reduced Elafin Levels Associated with Celiac Disease Bowel Inflammation

Levels of the enzyme elafin, an endogenous serine protease inhibitor, were lower in the small intestinal epithelium of patients with active celiac disease (CD) as compared to similar tissue from control patients.

Celiac disease is an immune disorder that occurs in susceptible individuals when foods that contain gluten and its derivative, the highly immunogenic gliadin peptide, trigger an immune response that leads to destruction of the intestinal lining, abdominal pain, changes in bowel habits, malnutrition and other symptoms that include anemia and neurological problems.

Investigators at McMaster University (Hamilton, ON, Canada; www.mcmaster.ca) used immunofluorescence techniques to examine the role of elafin in CD using tissues taken from human small intestines. The degree of deamidation of the 33-mer gliadin peptide was analyzed by liquid chromatography-mass spectrometry. To study the effects of elafin on a mouse model of celiac disease, the protein was delivered to the intestine of gluten-sensitive mice using a recombinant *Lactococcus lactis* vector.

Results published in the April 8, 2014, online edition of the *American Journal of Gastroenterology* revealed that elafin expression in the small intestinal epithelium was lower in patients with active CD compared with control patients. In vitro, elafin significantly slowed the kinetics of the deamidation of the 33-mer peptide to its more immunogenic form. Treatment of gluten-sensitive mice with elafin delivered by the *L. lactis* vector normalized inflammation and improved permeability.

Maintaining a gluten-free diet is far from simple, as gluten is found not only in foods but as low cost filler in the cosmetic and pharmaceutical industries as well.

"People who have to strictly avoid gluten for life often find this very difficult due to these hidden sources," said senior author Dr. Elena Verdu, associate professor of medicine at McMaster University. "There is a great need for a therapy that will protect patients with celiac disease from these accidental contaminations. The possibility of elafin administration or replacement as a new adjuvant therapy to the gluten free diet would add flexibility to a restrictive lifelong diet, and increase patients' quality of life and potentially accelerate the healing of celiac lesions."

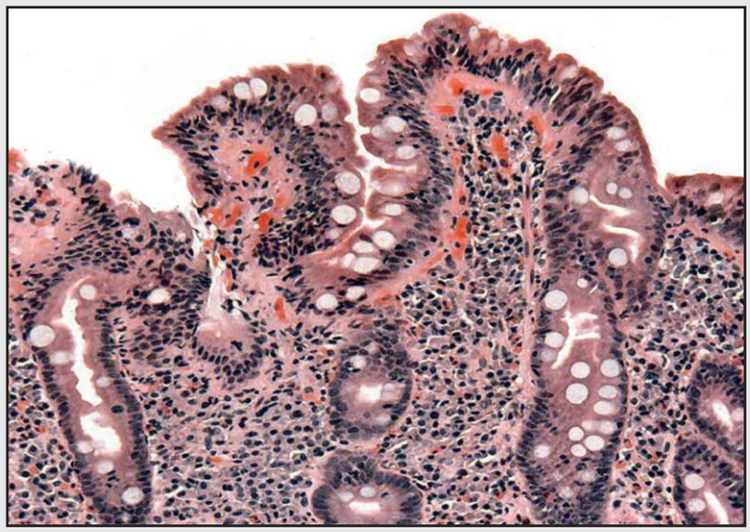


*Image: A biopsy of small bowel showing celiac disease manifested by blunting of villi, crypt hyperplasia, and lymphocyte infiltration of crypts (Photo courtesy of Wikimedia Commons).*

# Retinoic Acid Prevents Precancerous Breast Cells from Progressing to Full-Blown Cancer

Retinoic acid, a derivative of vitamin A, was found to prevent precancerous breast cells from progressing to full-blown cancer but did not have any effect on breast tumor cells.

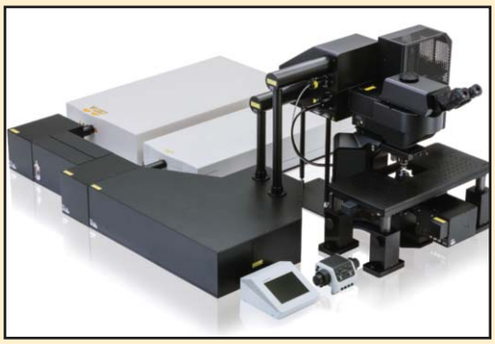
Investigators at Thomas Jefferson University (Philadelphia, PA, USA; www.jefferson.edu) worked with a novel breast cancer model that had been developed by treating MCF-10F human normal breast epithelial cells with a high dose of estradiol. The model system consisted of four distinct cell lines which demonstrated a progressive neoplastic transformation: MCF-10F, normal stage; trMCF, transformed MCF-10F; bsMCF, invasive stage; and caMCF, tumorigenic stage. In three-dimensional cultures, MCF-10F cells formed tubules resembling the structures in the normal mammary gland. After treatment with estradiol, these cells formed tubules and spherical masses, which were indicative of transformation.

In the current study the investigators evaluated the effect of all trans-retinoic acid (ATRA) at different stages of neoplastic transformation. Retinoids have been used as potential chemotherapeutic or chemopreventive agents because of their differentiative, antiproliferative, proapoptotic, and antioxidant properties.

Cells that only formed spherical masses in collagen were isolated (trMCF clone 11) and treated with ATRA. After treatment with a concentration of one micromolar ATRA, the trMCF clone 11 cells showed tubules in collagen. Gene expression studies showed that 207 genes upregulated in transformed trMCF clone 11 cells were downregulated after one micromolar ATRA treatment to levels comparable to those found in the normal breast epithelial cells MCF-10F. Furthermore, 236 genes that were downregulated in trMCF clone 11 were upregulated after one micromolar ATRA treatment to similar levels shown in normal epithelial cells. These 443 genes defined a signature of the ATRA reprogramming effect.

Results published in the March 21, 2014, edition of the *International Journal of Oncology* showed that one micromolar ATRA was able to redifferentiate transformed cells at early stages of the neoplastic process and antagonistically regulate breast cancer associated genes. On the other hand, the invasive and tumorigenic cells did not show any changes in morphology after ATRA treatment.

"It looks like retinoic acid exerts effects on cancer cells in part via the modulation of the epigenome," said senior author Dr. Sandra V. Fernandez, assistant research professor of medical oncology at Thomas Jefferson University. "We were able to see this effect of retinoic acid because we were looking at four distinct stages of breast cancer. It will be interesting to see if these results can be applied to patients."



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# Penny Contact Lenses Created from Clear Liquid

One droplet of clear liquid can bend light, acting as a lens. Now, by utilizing this well-known phenomenon, researchers have developed a new process to create inexpensive, high quality lenses that should cost less than USD 0.01 apiece.

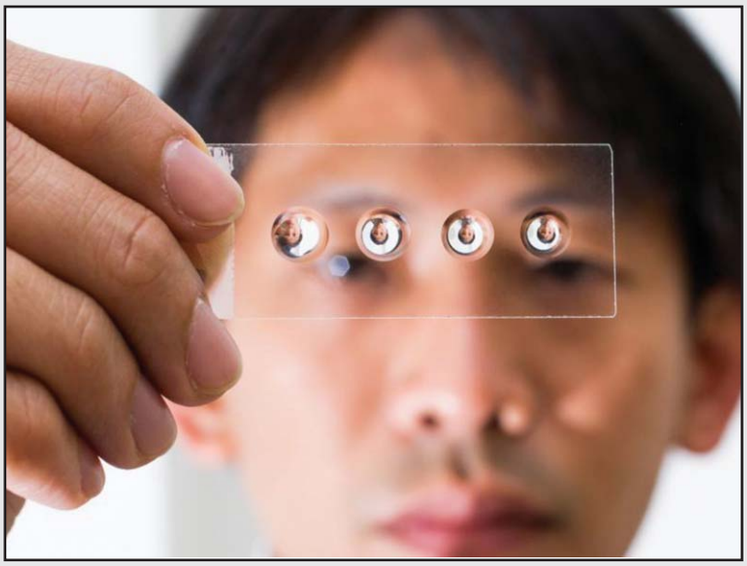
Because the lenses being so inexpensive, they can be used in a variety of applications, including tools to detect diseases in the field, scientific research in the lab and optical lenses and microscopes for education in classrooms.

"What I'm really excited about is that it opens up lens fabrication technology," stated Dr. Steve Lee from the Research School of Engineering at the Australian National University (ANU; Canberra, Australia; www.anu.edu.au) of the new technique, which he and his colleagues described in an article published April 24, 2014, in The Optical Society's (OSA) open-access journal *Biomedical Optics Express*.

Many conventional lenses are made the same way lenses have been made since Isaac Newton's day – by grinding and polishing a flat disk of glass into a specific curved shape. Others are produced with more sophisticated methods, such as pouring gel-like materials molds. But both approaches can be costly and complicated, according to Dr. Lee. With the new technology, the researchers harvest solid lenses of differing focal lengths by suspending and curing droplets of a gel-like material – a simple and inexpensive approach that avoids costly or complicated machinery. "What I did was to systematically fine-tune the curvature that's formed by a simple droplet with the help of gravity, and without any molds," he explained.

Although scientists have long known that a droplet can act as a lens, no one tried to see how good a lens it could be. Now, the team has developed a process that pushes this idea to its limits, according to the researchers. All that is required is an oven, a microscope glass slide, and a common, gel-like silicone polymer called polydimethylsiloxane (PDMS). First, a small amount of PDMS is dropped onto the slide. Then, it is baked at 70 °C to harden it, creating a base. Then, another squirt of PDMS is dropped onto the base and the slide is flipped over. Gravity pulls the new droplet down into a parabolic shape. The droplet is baked again to solidify the lens. More drops can then be added to hone the shape of the lens that also greatly increases the imaging quality of the lens. "It's a low cost and easy lens-making recipe," Dr. Lee said.

The researchers made lenses about a few millimeters thick with a magnification power of 160 times and a resolution of about 4 micrometers – two times lower in optical resolution than many commercial microscopes, but more than three orders of magnitude lower in cost. "We're quite surprised at the magnification enhancement using such a simple process," he noted.



Their low cost – low enough to make them disposable – allows for a variety of uses. In particular, the researchers have constructed a lens attachment that converts a smartphone camera into a dermascope, a tool to diagnose skin diseases such as melanoma. Whereas common dermascopes can cost USD 500 or more, the phone version costs approximately USD 2. The new dermascope, which was made using a three-dimensional (3D) printer and is designed for use in rural areas or developing countries, is slated to be commercially available in just a few months, according to Dr. Lee. A similar smartphone-based tool can also help farmers identify pests out in their fields.

Dr. Lee also foresees that the lenses could be used in the lab as implantable lenses that biologists can use to study cells in vivo. The high cost of conventional lenses usually dissuades scientists from implanting them into mice, he reported. The lenses would also be suitable for hobbyists or as part of low cost mobile microscopes that can be distributed to children and others for educational or outreach purposes, he added. "Simple optics can be very powerful."

So far, the researchers cannot make lenses much bigger than 1.27 cm in diameter. But to expand the range of applications, the investigators are now fine-tuning the process to make lenses as large as 5.08 cm and increasing the lens's optical performance.

*Image: A set of droplet lenses on a microscope coverslip held up by ANU researcher Steve Lee (Photo courtesy of Stuart Hay).*

# Bone Marrow-on-a-Chip Designed to Evaluate New Drugs, Radiation Toxicity

New organ-on-a-chip technology is providing scientists with an important new tool to assess the effects of new drugs and toxic agents on whole bone marrow. The device, nicknamed "bone marrow-on-a-chip," was developed by scientists from Harvard University's Wyss Institute for Biologically Inspired Engineering (SEAS; Boston, MA, USA; http://wyss.harvard.edu), and reproduces the functions, structure, and cellular composition of bone marrow, a complicated tissue that until now could only be studied intact in living animals, institute researchers reported in the May 4, 2014, online issue of the journal *Nature Methods*.

Specifically, the device could be used to develop safe and effective approaches to prevent or treat radiation's deadly effects on bone marrow without resorting to animal testing, a challenge that is being pursued at the Institute with funding support from the US Food & Drug Administration (FDA). In an initial test, the engineered bone marrow, similar to human marrow, shrunk in response to radiation unless a drug known to prevent radiation poisoning was present.

The bone marrow-on-a-chip in the future could also be employed to maintain a cancer patient's own marrow temporarily while he or she underwent marrow-damaging treatments such as radiation therapy or high-dose chemotherapy. "Bone marrow is an incredibly complex organ that is responsible for producing all of the blood cell types of our body, and our bone marrow chips are able to recapitulate this complexity in its entirety and maintain it in a functional form in vitro," said Don Ingber, MD, PhD, founding director of the Wyss Institute, a professor of vascular biology at Harvard Medical School and Boston Children's Hospital, and a professor of bioengineering at the Harvard School of Engineering and Applied Science (SEAS; http://seas.harvard.edu), and senior author of the study.

Dr. Ingber leads a large effort to develop human organs-on-chips. Up to now, Wyss Institute investigators have constructed lung, heart, kidney, and gut chips that reproduce basic characteristics of organ function, and they have more organs-on-chips in the works. The technology has been recognized internationally for its potential to replace animal testing of new drugs and environmental toxins, and as a new way for scientists to model human disease.

To build organ chips, the researchers have combined multiple types of cells from an organ on a microfluidic chip, while gradually supplying nutrients, removing waste, and applying mechanical forces the tissues would face in the body. But bone marrow is so complicated that they needed a new approach to mimic organ function.

This complexity arises because bone marrow has an essential relationship with bone. Marrow sits inside trabecular bone – a solid-looking type of bone with a porous, honeycombed interior. Some areas are warmer, some cooler; some are oxygen-rich, others oxygen-starved – and the dozen or so cell types each have their own preferred sites. To add complexity, bone marrow cells communicate with each other by secreting and sensing a range of biomolecules, which act locally to tell them whether to live, die, specialize or multiply.

Specifically, the researchers packed dried bone powder into an open, ring-shaped mold the size of a coin battery, and implanted the mold under the skin on the animal's back. After eight weeks, they surgically removed the disk-shaped bone that had formed in the mold and examined it with a specialized computed tomography (CT) imaging scanner. The scan revealed a honeycomb-like structure that looked the same as natural trabecular bone.

When they stained the tissue and examined it under a microscope, the marrow was packed with blood cells, similar to a marrow from a living mouse. Furthermore, when the researchers sorted the bone marrow cells by type and checked their numbers, the combination of different types of blood and immune cells in the modified bone marrow was identical to that in a mouse thighbone.

To maintain the engineered bone marrow outside of a living animal, the researchers surgically removed the engineered bone from mice, then placed it in a microfluidic device that steadily supplied nutrients and removed waste to mimic the circulation the tissue would experience in the body. Marrow in the device remained healthy for up to one week – long enough, typically, to test the toxicity and effectiveness of a new drug.

Bone marrow-on-a-chip could also generate blood cells, which could circulate in an artificial circulatory system to supply a network of other organs-on-chips. The US Defense Agency Advanced Research Projects Agency (DARPA) is also currently providing funds to the Wyss Institute to develop an interconnected network of ten organs on chips to study complex human physiology outside the body.

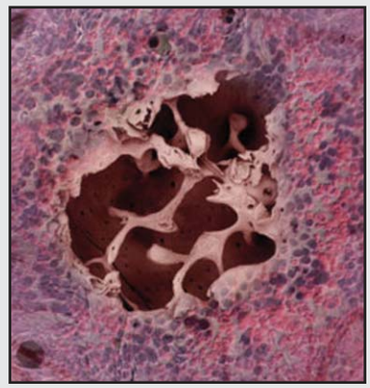


*Image: Microscopic view of the engineered bone with an opening exposing the internal trabecular bony network, overlaid with colored images of blood cells and a supportive vascular network that fill the open spaces in the bone marrow-on-a-chip (Photo courtesy of James Weaver / Harvard University, Wyss Institute for Biologically Inspired Engineering).*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# Unanticipated Link Found Between Cell Suicide and Long Life

Many health professionals believe that free radicals, the occasionally toxic molecules generated by the body as it processes oxygen, are the cause behind aging. However, a number of studies recently have generated evidence that the contrary may be true.

Researchers from McGill University (Montreal, QC, Canada; www.mcgill.ca) have taken this finding further by showing how free radicals promote longevity in a research model organism, the roundworm *Caenorhabditis elegans*. Unexpectedly, the scientists discovered that free radicals (i.e., oxidants) act on a molecular mechanism that, in other surroundings, instructs a cell to kill itself.

Apoptosis is a process by which injured cells commit suicide in a range of circumstances: to avoid inducing autoimmune disease, to avoid becoming cancerous, or to kill off viruses that have invaded the cell. The key molecular mechanism by which this occurs is well conserved in all animals, but was first discovered in *C. elegans* – a finding that earned a Nobel Prize.

The McGill University researchers discovered that this same mechanism, when stimulated in the correct manner by free radicals, in reality strengthens the cell's defenses and increases its longevity. Their findings were published online May 8, 2014, in the journal *Cell*. "People believe that free radicals are damaging and cause aging, but the so-called 'free radical theory of aging' is incorrect," said Siegfried Hekimi, a professor in McGill's department of biology, and senior author of the study. "We have turned this theory on its head by proving that free radical production increases during aging because free radicals actually combat – not cause – aging. In fact, in our model organism we can elevate free radical generation and thus induce a substantially longer life."

The findings have significant ramifications. "Showing the actual molecular mechanisms by which free radicals can have a pro-longevity effect provides strong new evidence of their beneficial effects as signaling molecules," Prof. Hekimi said. "It also means that apoptosis signaling can be used to stimulate mechanisms that slow down aging. Since the mechanism of apoptosis has been extensively studied in people, because of its medical importance in immunity and in cancer, a lot of pharmacological tools already exist to manipulate apoptotic signaling. But that doesn't mean it will be easy."

Triggering pro-longevity apoptotic signaling could be especially critical in neurodegenerative disorders, according to Prof. Hekimi. "In the brain the apoptotic signaling might be particularly tilted toward increasing the stress resistance of damaged cells rather than killing them. That's because it is harder to replace dead neurons than other kinds of cells, partly because of the complexity of the connections between neurons."

*Image: The roundworm Caenorhabditis elegans, used as an experimental model organism for researchers who showed how free radicals promote longevity (Photo courtesy of McGill University).*

# Experimental Drug Protects Animal Model from Measles-Like Virus

Working with an animal model that mimics measles in humans, a team of molecular virologists has verified that a novel antiviral drug may complement the currently used vaccine and lead to eradication of the disease.

To better study the measles virus under laboratory conditions investigators at Georgia State University (Atlanta, USA; www.uga.edu) and colleagues at Emory University (Atlanta, GA, USA; www.emory.edu) and the Paul-Ehrlich Institute (Langen, Germany; www.pei.de) used zoonotic *Canine distemper virus* (CDV), which induces a disease in ferrets with 100% lethality.

The investigators used the ferret model to evaluate the experimental drug ERDRP-0519, which targets the viral RNA polymerase. This enzyme is required for replication of the virus, as it catalyzes the synthesis of a complementary strand of RNA from the original viral RNA template.

Results reported in the April 16, 2014, issue of the journal *Science Translational Medicine* revealed that prophylactic oral drug treatment of the ferrets protected them from a lethal dose of CDV administered intranasally. Ferrets that received the drug after having been infected with the same dose of virus showed low-grade viral loads, remained asymptomatic, and recovered from infection, whereas control animals succumbed to the disease. Animals that had recovered from CDV infection demonstrated a robust immune response and were protected against re-challenge with a lethal CDV dose.

The investigators stated that the drug is not intended as a substitute for vaccination, but as an additional weapon in a concerted effort to eliminate the disease. "The emergence of strong antiviral immunity in treated animals is particularly encouraging, since it suggests that the drug may not only save an infected individual from disease but contribute to closing measles immunity gaps in a population," said senior author Dr. Richard Plemper, professor in the center for inflammation, immunity, and infection at Georgia State University.

# Project to Move Engineered Tissue and Organs from Lab to the Bedside or Operating Room

As developments in lab-created organs and tissues continue to advance, the challenge becomes how to translate the technology from the laboratory to the operating room. Two US universities are now exploring manufacturing platforms to mass produce customized engineered tissues and organs.

Developing a way to scale up personalized lab-created organs and tissues would benefit patients around the world who must wait for donated organs to receive transplants. North Carolina (NC) State University's (Raleigh, NC, USA; www.ise.ncsu.edu) industrial and systems engineering department (NC State ISE) engineers are partnering with biomedical scientists at the Wake Forest Institute for Regenerative Medicine (WFIRM; Winston-Salem, NC, USA; www.wakehealth.edu/WFIRM). Together, the institutions are creating advancements in 3D technology, computer-aided modeling and intelligent automation to print tissues and organs for patients. With their focus on precision, computer modeling and three-dimensional (3D) printing will help scientists scale up the tissue engineering processes currently being done manually.

The future of organs-on-demand requires the mass generation of precise parts that are specific to each individual recipient. The development entails combining the cells and a scaffold, or a model that forms the essential shape. The support structure is designed to gradually dissolve after implantation in the body. At the same time, the scaffolding material is being absorbed by the body, and the cells lay down materials to form a permanent support structure, progressively replacing the engineered scaffold with a new organ.

Leading corporate and education specialists in medicine, engineering, and science gathered at this year's Regenerative Medicine Foundation Conference, May 5-7, 2014, held in San Francisco (CA, USA), to share firsthand accounts of their visions and challenges of bio-tissue manufacturing. Dr. Binil Starly, director of NC State ISE's laboratory for engineering biological tissue systems, uses bioprinting to devise ways for mass producing engineered tissue and also shared data about these latest developments, including a patent-pending process, which is collaboration between WFIRM and NCSU, for providing replacement skin for burn victims.

"It is one thing to be able to grow an organ but another to take that ability to the bedside, so involving manufacturing engineers early on in the biological research phase is vital to achieving commercialization," said Dr. Starly. "NC State ISE reviews the scientific process for growing tissue cells, and then applies 3D technologies and algorithms to automate it, so a very sensitive biological process can be replicated safely and effectively."

Dr. Anthony Atala, director of WFIRM and NC State ISE advisory board member, moderated a panel on the marketing of regenerative medicine therapies at the conference. WFIRM scientists have developed lab-grown organs, such as bladders, vaginal organs, and urine tubes successfully used in patients.

*Image: Laboratory-grown vaginas. The procedure offers hope to women with congenital conditions in which the vagina and uterus are underdeveloped (Photo courtesy of Francois Lenoir / Reuters).*

## 3D Test Reduces Dependence On Lab Animals for Testing Asthma and Allergy Agents

In a recent study, scientists report that they've developed a simple, three-dimensional (3D) laboratory technique to test asthma and allergy medications that mimics what occurs in the body, which could help reduce the need for animal testing.

Dr. Amir Ghaemmaghami and colleagues from the University of Nottingham (UK; www.nottingham.ac.uk) noted that respiratory disorders, such as asthma and allergies, are becoming more common. These conditions affect the lungs and the airway leading to the lungs, making it difficult to breathe. Respiratory symptoms lead to expensive hospital visits, as well as absences from work and school. Improved agents could provide better relief, but before giving new medicines to people, researchers must first test them in animals – an expensive and arduous process. Sometimes, researchers will use 2D tests in which they apply the drug to a layer of human cells in a lab dish instead, but this is not a satisfactory way to tell how a pharmaceutical agent will perform in a whole animal or a whole individual. Therefore, Dr. Ghaemmaghami's team developed a new, 3D alternative.

Their test includes three types of human cells that are typically in a person's airway. In the body, these cells are close together and are involved in the development of respiratory conditions. The 3D model reacted similar to an actual person's airway when they exposed it to allergens and bacterial extract. They say that the model has the potential of reducing the need for some animal testing of new drugs for respiratory conditions.

The study's findings were published March 14, 2014, in the ACS' journal *Molecular Pharmaceutics.*

# Novel Technique Allows Genome Sequencing of Single Malaria Cells

A recently developed technique for analyzing the genome of a malaria parasite within a single red blood cell is expected to aid in the understanding of the molecular cell biology of these organisms and in the design of new drugs to prevent their growth and spread.

Investigators at the Texas Biomedical Research Institute (San Antonio, USA; http://txbiomed.org) combined advanced cell sorting technology and whole-genome amplification (WGA) to generate high-quality DNA samples from parasite-infected red blood cells (RBCs) for genotyping and next-generation sequencing. They optimized this approach through analysis of more than 260 single-cell assays, and quantified accuracy by decomposing mixtures of known parasite genotypes and obtaining highly accurate (> 99%) single-cell genotypes.

The investigators applied this validated approach directly to infections of two major malaria species, *Plasmodium falciparum*, for which long term culture is possible, and *Plasmodium vivax*, for which no long-term culture is feasible. They demonstrated that the single-cell genomics approach could be used to generate parasite genome sequences directly from patient blood in order to unravel the complexity of *P. vivax* and *P. falciparum* infections.

Malaria parasite infections are complex and often contain multiple different parasite genotypes and even different parasite species. "This has really limited our understanding of malaria parasite biology" said senior author Dr. Ian Cheeseman, a postdoctoral scientist in the genetics department of the Texas Biomedical Research Institute. "It is like trying to understand human genetics by making DNA from everyone in a village at once. The data is all jumbled up – what we really want is information from individuals. We are now able to look at malaria infections with incredible detail. This will help us understand how to best design drugs and vaccines to tackle this major global killer."

The study describing the novel single-cell approach for genome sequencing was published in the May 8, 2014, online edition of the journal *Genome Research.*

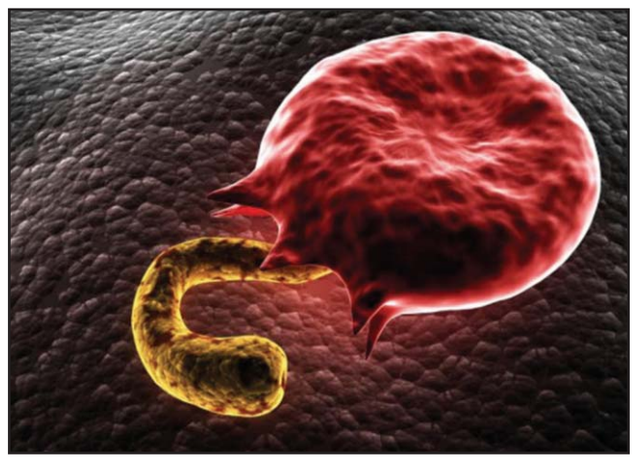

*Image: The malaria parasite invading a red blood cell (Photo courtesy of Shutterstock).*

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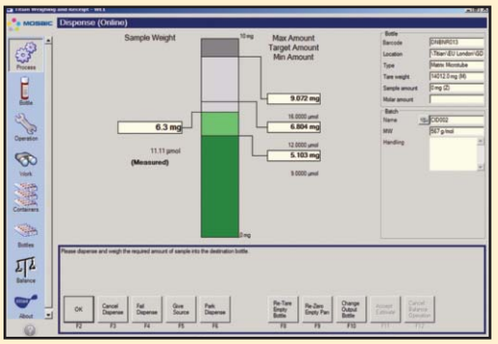


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# Encapsulated Human-Insulin-Producing Progenitor Cells Cure Diabetes in Mouse Model

A breakthrough system that allows subcutaneous implantation of encapsulated immature pancreatic cells (beta progenitor cells) was shown to produce enough insulin to correct the symptoms of diabetes in a mouse model.

Investigators at the Sanford-Burnham Medical Research Institute (La Jolla, CA, USA; www.sanfordburnham.org) and the University of California, San Diego (USA; www.ucsd.edu) placed CyT49 pancreatic islets derived from human embryonic stem cells (hESCs) into TheraCyte (Laguna Hills, CA, USA; www.theracyte.com) encapsulation devices and transplanted the devices into a diabetic mouse model.

The TheraCyte system for encapsulating and transplanting cells is a thin membrane-bound polymeric chamber. It is fabricated from biocompatible membranes, which protect allogeneic cells from rejection by the recipient and, when implanted subcutaneously, induce the development of blood capillaries close to the membranes. This vascularization feature provides a rich blood supply to nourish the tissues within the membranes, aids in the communication of implanted cells with the host, and assures rapid uptake of therapeutic molecules. The TheraCyte system is protected by 20 US patents and multiple foreign patent filings in Europe and Japan.

The investigators monitored human insulin secretion and employed bioluminescent imaging to evaluate the maturation, growth, and containment of the encapsulated islet progenitors. They reported in the March 24, 2014, online edition of the journal *Stem Cell Research* that human insulin was detectable by seven weeks post-transplant and increased 17-fold over the course of eight weeks, yet during this period the biomass of encapsulated cells remained constant. Remarkably, by 20 weeks post-transplant encapsulated cells secreted sufficient levels of human insulin to ameliorate alloxan induced diabetes. Furthermore, bioluminescent imaging revealed that hESCs remained fully contained in the encapsulation device for up to 150 days, the longest period tested.

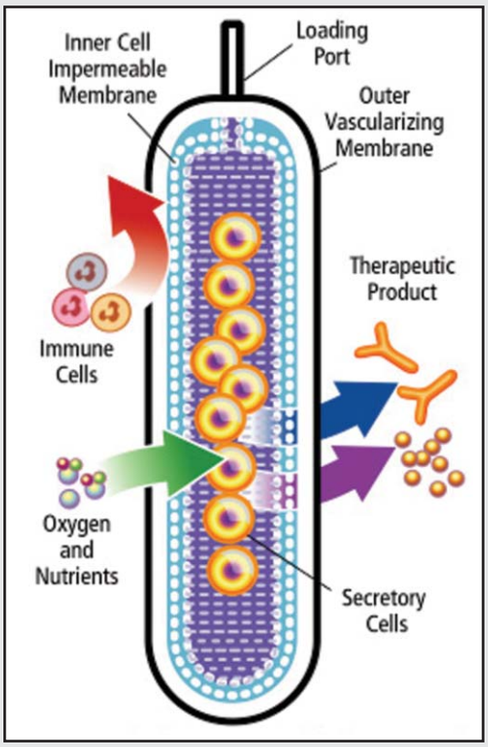


*Image: The TheraCyte system for encapsulating and transplanting cells is a thin membrane bound polymeric chamber. It is fabricated from biocompatible membranes, which protect allogeneic cells from rejection by the recipient and, when implanted subcutaneously, induce the development of blood capillaries close to the membranes (Photo courtesy of TheraCyte).*

# Vitamin D May Raise Survival Rates Among Cancer Patients

Cancer patients who have higher levels of vitamin D when they are diagnosed are inclined to have better survival rates and remain in remission longer than patients who are vitamin D-deficient, according to new research.

The findings are scheduled for publication in the July 2014 issue of the Endocrine Society's *Journal of Clinical Endocrinology & Metabolism (JCEM)*. The body naturally produces vitamin D after exposure to sunlight and absorbs it from specific foods. Vitamin D affects a variety of biologic mechanisms by binding to a protein called a vitamin D receptor, in addition to helping the body absorb the calcium and phosphorus required for healthy bones. This receptor is present in nearly every cell in the body.

"By reviewing studies that collectively examined vitamin D levels in 17,332 cancer patients, our analysis demonstrated that vitamin D levels are linked to better outcomes in several types of cancer," said one of the study's authors, Hui Wang, MD, PhD, a professor of the Institute for Nutritional Sciences at the Shanghai Institutes for Biological Sciences at the Chinese Academy of Sciences (Shanghai, China; http://sibs.cas.cn). "The results suggest vitamin D may influence the prognosis for people with breast cancer, colorectal cancer and lymphoma, in particular."

The meta-analysis looked at the findings of 25 individual studies that measured vitamin D levels in cancer patients at the time of diagnosis and monitored survival rates. In most of the research, patients had their vitamin D levels tested before they underwent any treatment for cancer. The study found a 10 nmol/L increase in vitamin D levels was tied to a 4% increase in survival among cancer patients.

Researchers found the strongest association between vitamin D levels and survival in breast cancer, lymphoma and colorectal cancer. There was less evidence of a connection in people with Merkel cell carcinoma, lung cancer, gastric cancer, prostate cancer, leukemia, or melanoma but the available results were positive.

# Chitosan Treatment Clears Way for Antibiotics To Eliminate Recurrent Urinary Tract Infections

*Image: Commercial chitosan is derived from the shells of shrimp and other sea crustaceans, including Pandalus borealis, pictured here (Photo courtesy of Wikipedia).*

Recurrent urinary tract infection was successfully resolved in a mouse model by treatment with the exfoliant chitosan followed by a round of antibiotics.

Bacterial urinary tract infection (UTI), most commonly caused by uropathogenic *Escherichia coli* (UPEC), can affect the kidneys, bladder, uretha or ureters. These bacteria usually are susceptible to antibiotics, but they can to pass through the surface layer of cells lining the bladder and colonize deeper layers of cells and tissue where they lie dormant and are protected from destruction by antibiotics. These reservoirs are a potential source for the recurrent UTIs that affect millions of individuals annually.

Investigators at the University of Utah (Salt Lake City, USA; www.utah.edu) used the exfoliant chitosan to remove the surface layer of bladder cells. Chitosan is a deacetylated derivative of chitin, which is the structural element in the exoskeleton of crustaceans (such as crabs and shrimp) and cell walls of fungi. It is being developed for a number of industrial, agricultural, and biomedical uses, including drug and vaccine delivery in animals and humans. A common method for the synthesis of chitosan is the deacetylation of chitin using sodium hydroxide in excess as a reagent and water as a solvent. On average, the molecular weight of commercially produced chitosan is between 3.8 and 20.0 kDa.

The investigators found that when instilled for 20 minutes into the bladders of mice via catheterization, chitosan disrupted tight junctions and caused rapid exfoliation of the superficial epithelial cells without eliciting overt signs of inflammation. By inducing the exfoliation of the superficial layers of the urothelium, chitosan stimulated rapid regenerative processes and induced the reactivation of dormant intracellular UPEC populations. Upon removal of chitosan, the permeability barrier function of the urothelium was restored within several hours, and the tissue was completely regenerated within about a week.

Working with a mouse model of recurrent UTI, the investigators followed up chitosan treatment by giving the animals a one-week course of fluoroquinolones, an antibiotic class commonly used to treat UTIs. They reported in the March 25, 2014, online edition of the journal *PLOS ONE* that examination of the mice one week after antibiotic treatment revealed that the reservoir UPEC populations had for the most part been eliminated.

"Effectively, there were no bacteria in the bladder," said Dr. Matthew Blango, a postdoctoral researcher at the University of Utah. "Antibiotics do not do a good job of getting rid of reservoir populations, but when augmented with chitosan, there was a significant reduction in the level of bacteria in mouse bladders."

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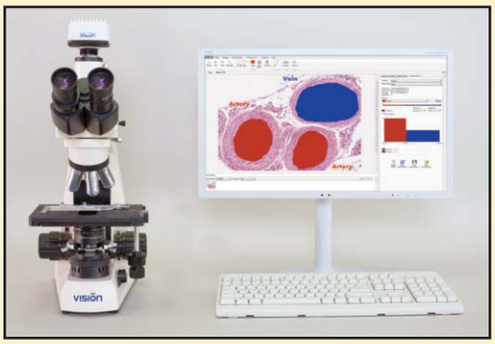

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The Raman Imaging and Scanning Electron (RISE) microscope combines a stand-alone electron microscope and confocal Raman microscope. Using RISE microscopy, ultrastructural and molecular images of a sample can be generated and correlated with one instrument.

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# Stem Cells Loaded with Oncolytic Herpes Virus Destroy Brain Tumors in Mouse Model

Cancer researchers treated mouse models of the human brain tumor glioblastoma multiforme by injecting the animals with stem cells loaded with oncolytic herpes virus and treated virus-resistant tumors with oncolytic herpes viruses genetically engineered to express the proapoptotic cytokine TRAIL.

Glioblastoma multiforme (GBM) is an aggressive brain tumor, fatal within one year from diagnosis in most patients despite intensive treatment with surgery, radiation, and chemotherapy. The migratory and microscopically invasive nature of GBM as well as its resistance to chemotherapy renders conventional therapies inadequate in its treatment. Attempts to treat GMB with oncolytic viruses have been unsuccessful mainly because of insufficient viral spread after tumor resection.

Investigators at Harvard University (Cambridge, MA, USA; www.harvard.edu) loaded human mesenchymal stem cells (MSC) with oncolytic herpes simplex virus (MSC-oHSV), and the fate of the stem cells following injection into mice was followed by real-time imaging in vitro and in vivo. The efficacy of MSC-oHSV and its proapoptotic variant, oHSV-TRAIL (tumor necrosis factor-related apoptosis-inducing ligand) encapsulated in synthetic extracellular matrix (sECM), was tested in different mouse GBM models, which more accurately reflected the current clinical settings of malignant, resistant, and resected tumors.

TRAIL is a cytokine that is produced and secreted by most normal tissue cells. It causes apoptosis primarily in tumor cells by binding to certain death receptors. Since the mid-1990s it has been used as the basis for several anticancer drugs, but was not been found to have any significant survival benefit.

Results published in the June 2014 online edition of the *Journal of the [US] National Cancer Institute* revealed that the MSC-oHSVs effectively produced oHSV progeny, which resulted in killing of GBMs in vitro and in vivo mediated by a dynamic process of oHSV infection and tumor destruction. sECM-encapsulated MSC-oHSVs resulted in statistically significant increased anti-GBM efficacy compared with direct injection of purified oHSV in a preclinical model of GBM resection, resulting in prolonged median survival of the mice. In a model of virus resistant tumors, it was seen that MSCs loaded with oHSV-TRAIL effectively induced apoptosis-mediated killing and prolonged median survival of the mice.

"Our approach can overcome problems associated with current clinical procedures," said senior author Dr. Khalid Shah, professor of medicine at Harvard University. "The work will have direct implications for designing clinical trials using oncolytic viruses, not only for brain tumors, but for other solid tumors. We know that 70%–75% of glioblastoma patients undergo surgery for tumor debulking, and we have previously shown that MSCs encapsulated in biocompatible gels can be used as therapeutic agents in a mouse model that mimics this debulking. So, we loaded MSCs with oncolytic herpes virus and encapsulated these cells in biocompatible gels and applied the gels directly onto the adjacent tissue after debulking. We then compared the efficacy of virus-loaded, encapsulated MSCs versus direct injection of the virus into the cavity of the debulked tumors. They survived because the virus does not get washed out by the cerebrospinal fluid that fills the cavity. Previous studies that have injected the virus directly into the resection cavity did not follow the fate of the virus in the cavity. However, our imaging and side-by-side comparison studies showed that the naked virus rarely infects the residual tumor cells. This could give us insight into why the results from clinical trials with oncolytic viruses alone were modest."

*Image: The oncolytic herpes simplex virus (oHSV) appeared to have so much potential against malignant glioblastoma multiforme, the most common brain tumor in human adults, that researchers looked for a way to increase its staying power (Photo courtesy of Khalid Shah, Ph.D., Harvard University / Sebastian Kaulitzki, Fotolia).*

# 3D Printed Cancer Cells Mimic Tumors

A group of Chinese and American researchers have successfully created a three-dimensional (3D) model of a cancerous tumor using a 3D printer. The model, which consists of a scaffold of fibrous proteins coated in cervical cancer cells, has provided an accurate 3D representation of a tumor's environment and could help in the discovery of new drugs and cast new light on how tumors develop, grow, and metastasize throughout the body.

The study's findings were published April 11, 2014, in the Institute of Physics (IOP) Publishing's journal *Biofabrication*. The model consists of a grid structure, 10 mm in width and length, composed of gelatin, alginate, and fibrin, which recreates the fibrous proteins that make up the extracellular matrix of a tumor.

The grid structure is coated in Hela cells – an unusual, "immortal" cell line that was first derived from a cervical cancer patient in 1951. Because the cells' ability to divide forever in a laboratory setting, the cell line has been used in some of the most substantial scientific studies of the past 50 years.

Although the most effective approach to studying tumors is to do so in a clinical trial, ethical and safety restrictions make it hard for these types of studies to be performed on a wide scale. To overcome this, 2D models, consisting of a single layer of cells, have been created to mimic the physiologic environment of tumors so that different types of drugs can be evaluated in a realistic manner. With the dawn of 3D printing, it is now possible to provide a more realistic representation of the environment surrounding a tumor, which the researchers have demonstrated in this study by comparing results from their 3D model with results from a 2D model.

In addition to assessing if the cells remained viable (alive) after printing, the researchers also examined how the cells proliferated, how they expressed a specific set of proteins, and how resistant they were to anticancer agents. The proteins examined were part of the matrix metalloproteinases (MMP) protein family. These proteins are used by cancer cells to break through their surrounding matrix and help tumors to spread. Resistance to anticancer drugs, which was also studied, is a good indicator of tumor malignancy.

The findings revealed that 90% of the cancer cells remained viable after the printing process. The findings also demonstrated that the 3D model had more similar characteristics to a tumor compared to 2D models and in the 3D model the cancer cells showed a higher proliferation rate, higher protein expression and higher resistance to anticancer drugs.

The lead author of the research, Prof. Wei Sun, from Tsinghua University (Beijing, China; www.tsinghua.edu.cn), and Drexel University (Philadelphia, PA, USA; www.drexel.edu), said, "We have provided a scalable and versatile 3D cancer model that shows a greater resemblance to natural cancer than 2D cultured cancer cells. With further understanding of these 3D models, we can use them to study the development, invasion, metastasis and treatment of cancer using specific cancer cells from patients. We can also use these models to test the efficacy and safety of new cancer treatment therapies and new cancer drugs."

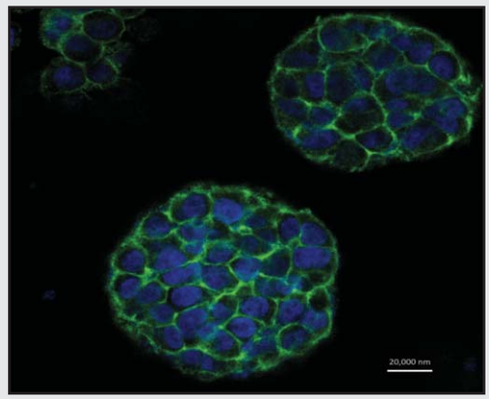


*Image: The 3-D tumor cellular morphology on day 8 of testing (Photo courtesy of the Institute of Physics).*

# Epigenomic Mapping Highlights Differences Between Ancient and Modern Humans

Molecular biologists employing advanced epigenetic techniques have identified genetic differences between *Homo sapiens* and extinct types of humans such as Neanderthals and Denisovans that are linked to modern diseases like Alzheimer's disease, autism, and schizophrenia.

Epigenomics is the study of the complete set of epigenetic modifications on the genetic material of a cell, known as the epigenome. The field is analogous to genomics and proteomics, which are the study of the genome and proteome of a cell. Epigenetic modifications are reversible modifications to a cell's DNA or histones that affect gene expression without altering the DNA sequence. Two of the most characterized epigenetic modifications are DNA methylation and histone modification. Epigenetic modifications play an important role in gene expression and regulation, and are involved in numerous cellular processes such as in differentiation/development and tumorigenesis. Recent advances in high-throughput analytical technology have enabled rapid advances in epigenomic research.

The evolution of epigenetic regulation along the human lineage remains largely unexplored. To shed further light on this topic, investigators at the Hebrew University of Jerusalem (Israel; www.huji.ac.il) and their colleagues at the Max Planck Institute for Evolutionary Anthropology (Leipzig, Germany; www.eva.mpg.de) reconstructed the full DNA methylation maps of the Neandertal and the Denisovan by harnessing the natural degradation processes of methylated and unmethylated cytosines.

The investigators reported in the April 17, 2014, online edition of the journal *Science* that by comparing these ancient methylation maps to those of present-day humans, they had identified nearly 2000 differentially methylated regions (DMRs). Particularly, they found substantial methylation changes in the HOXD cluster that may explain anatomical differences between archaic and present-day humans. Hox genes (from an abbreviation of homeobox) are a group of related genes that control the body plan of the embryo along the anterior-posterior axis. After the embryonic segments have formed, the Hox proteins determine the type of segment structures (e.g., legs, antennae, and wings in fruit flies or the different types of vertebrae in humans) that will form on a given segment.

Additionally, the investigators found that DMRs were significantly more likely to be associated with modern diseases such as Alzheimer's disease, autism and schizophrenia, suggesting that recent epigenetic changes in brain tissues may underlie some of today's common psychiatric disorders.

The authors concluded by saying, "This study provides insight into the epigenetic landscape of our closest evolutionary relatives and opens a window to explore the epigenomes of extinct species."

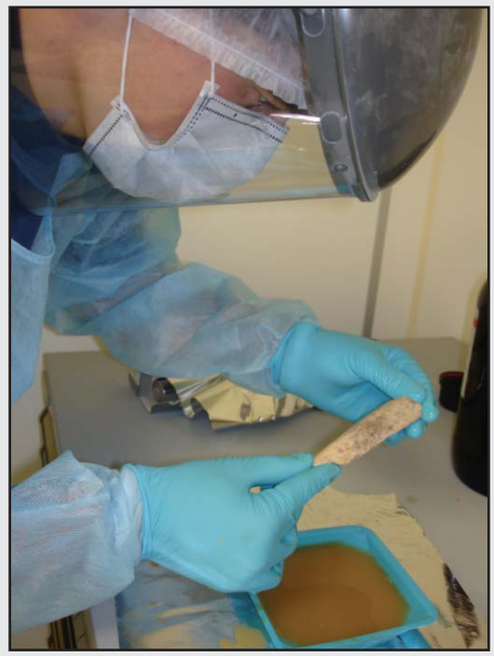

*Image: Working in a clean room, researchers took extensive precautions to avoid contaminating Neanderthal DNA samples - extracted from bones like this one - with DNA from any other source, including modern humans (Photo courtesy of the Max Planck Institute for Evolutionary Anthropology).*

# Actin-Binding Surface on Vinculin Mediates Mechanical Aspects of Cell Movement

A team of cell biologists has obtained data that shows how two proteins, vinculin and actin, function in concert to regulate cell morphology, motility, and mechanotransduction (the conversion of mechanical signals into electrical or chemical signals) and play a critical role in metastasis.

Vinculin is a cytoskeletal scaffold protein essential for embryogenesis and cardiovascular function. It localizes to focal adhesions and adherens junctions, where it connects cell surface receptors to the actin cytoskeleton. While vinculin interacts with many adhesion proteins, its interaction with filamentous actin regulates cell morphology, motility, and mechanotransduction.

Investigators at the University of North Carolina (Chapel Hill, USA; www.unc.edu) used negative-stain electron microscopy, discrete molecular dynamics techniques, and mutagenesis to develop a new model to explain the interaction between vinculin and actin. A major breakthrough in this effort was the development of mutated versions of vinculin that disrupted the actin/vinculin interaction in specific and traceable fashion.

Results published in the April 2014 online edition of the journal *Structure* revealed that actin-binding deficient vinculin variants expressed in vinculin knockout fibroblasts failed to correct cell-spreading defects and reduced cellular response to external force. These findings highlighted the importance of this actin-binding surface and provided the molecular basis for elucidating additional roles of this interaction, including actin-induced conformational changes that promoted actin bundling.

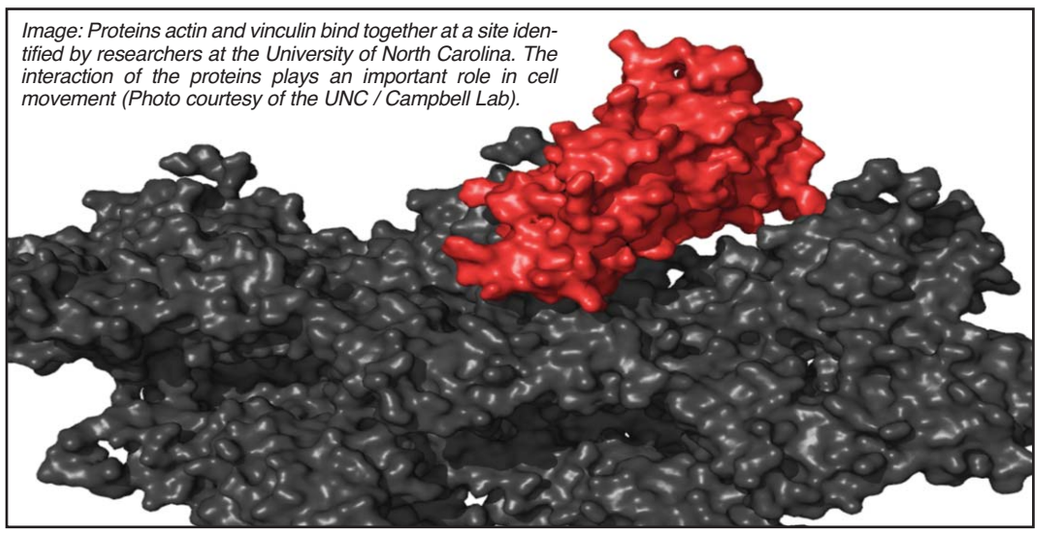

*Image: Proteins actin and vinculin bind together at a site identified by researchers at the University of North Carolina. The interaction of the proteins plays an important role in cell movement (Photo courtesy of the UNC / Campbell Lab).*

"Our data suggest that there is a face on the vinculin tail that has been ignored by the previous model, and that it is very important," said first author Peter Thompson, a graduate researcher at the University of North Carolina. "In your cardiovascular system – your heart and arteries – the cells that form these organs need to stick together tightly. They do these in part by forming cell-to-cell adherens junctions. Vinculin creates a critical physical link between the actin cytoskeleton and these junctions. If you disrupt that, the hypothesis is that cells no longer respond appropriately to force and the organ suffers."

"Our data supported a unique surface that was important for actin binding," said senior author Dr. Sharon Campbell, professor of biochemistry and biophysics at the University of North Carolina. "Identification of this actin binding surface on vinculin has enabled us to dissect how this critical interaction controls how cells respond to force and move. This in turn, will help us better understand how dysregulation leads to disease."

## Cancer Immunotherapy Sector to Surge to USD 9 Billion Across Major Pharma Through 2022

The immunotherapy market will experience substantial growth through 2022, increasing from USD 1.1 billion in 2012 to nearly USD 9 billion in 2022 (corresponding to 23.8% annual growth) in the United Kingdom, United States, France, Germany, Italy, Spain, and Japan, according to recent market research.

This notable growth will be fueled by the anticipated market entry of nine novel immunotherapies--including four novel immune checkpoint inhibitors and five novel therapeutic vaccines – in new oncology indications and/or patient populations, according to Decision Resources Group (Burlington, MA, USA; www.decisionresources.com). Combined, Bristol-Myers Squibb's anti-CTLA-4 agent Yervoy and innovative immune checkpoint inhibitors that target the anti-programmed cell death-1/programmed death-ligand-1 (PD-1/PD-L1) pathway – including Bristol-Myers Squibb/Ono Pharmaceutical's nivolumab, Merck & Co.'s pembrolizumab (MK-3475), Roche/Genentech/Chugai's MPDL-3280A and AstraZeneca/MedImmune's MEDI4736 – should dominate the immunotherapy market and capture a remarkable 85% market share in 2022.

## Abbott Selling Developed Market Generics Portfolio

Abbott Laboratories (Abbot Park, IL, USA; www.abbott.com) has sold its developed market generic drugs business to Mylan (Canonsburg, PA, USA; www.mylan.com) in a deal worth USD 5.3 billion.

The sale to Mylan will be in the form of an equity ownership of a newly formed entity, to be named Mylan NV, in which Abbott will have a stake of 21%. The new entity will be based in the Netherlands to achieve tax savings. Mylan NV will combine Mylan's existing business and Abbott's developed markets pharmaceuticals business, which includes Europe, Japan, Canada, Australia, and New Zealand, as well as manufacturing facilities in France and Japan. The transaction will diversify Mylan's business and strengthen its commercial platform outside the US (the US sector is not included).

The assets, which are being acquired on a debt-free basis, include a portfolio of more than 100 specialty and branded generic pharmaceutical products in five major therapeutic areas – central nervous system/pain, cardio/metabolic, gastrointestinal, anti-infective/respiratory, and women's and men's health – and also includes several patent protected, novel, and hard-to-manufacture products with continued growth potential.

Abbott will retain its branded generics pharmaceuticals business and products in emerging markets, where demographics and growing healthcare systems are combining to create an increased rate of patient access to healthcare, and where the majority of healthcare products are paid for directly by the consumer. Abbott will also retain manufacturing facilities in emerging markets as well as those situated in the Netherlands, Germany, and Canada.

## IDT Acquires Nuclease Product Line

The Surveyor line is to be used by Integrated DNA Technologies (IDT; Coralville, IA, USA; www.idtdna.com) primarily to support researchers performing mutation detection and potentially-clinical genome editing, and by Transgenomic, Inc. (Omaha, NE, USA; www.transgenomic.com) primarily to support diagnostic and other clinical applications.

IDT, a world leader in custom nucleic acid synthesis, is expanding its offerings by adding the Surveyor enzyme and kits of Transgenomic, a global company advancing diagnostics, cytogenetics, and specialized clinical and research services. As part of the agreement, IDT will acquire the Surveyor product line and intellectual property. Transgenomic will receive an exclusive license for clinical and diagnostic use of Surveyor products from IDT. Additional terms of the acquisition were not disclosed.

The key component of Surveyor products is Surveyor Nuclease, a member of the CEL nuclease family of mismatch-specific nucleases isolated from celery. Surveyor Nuclease has been shown to recognize and cleave mismatches arising from single nucleotide polymorphisms or small insertions or deletions.

## Teva Acquisition to Expand Pain Care Offerings

Teva Pharmaceutical Industries, Ltd. (Petach Tikva, Israel; www.tevapharm.com) will acquire Labrys Biologics, Inc. (San Mateo, CA, USA; www.labrysbiologics.com). The acquisition will broaden Teva's array of biotechnology assets and capabilities.

Teva will purchase Labrys for USD 200 million in upfront payment in cash at closing as well as up to USD 625 million in contingent payments upon achievement of certain pre-launch milestones. Potential peak sales for LBR-101 are estimated to reach USD 2–3 billion. With the goal of becoming a global leader in pain by 2020, the Labrys acquisition adds a significant migraine prophylaxis dimension to Teva's extensive pain care franchise, which includes a range of investigational, approved, and marketed treatments for migraine, cancer pain, and chronic pain.

Labrys is developing LBR-101, a fully humanized monoclonal antibody that binds to calcitonin gene-related peptide (CGRP) currently in phase IIb clinical trials for prevention of chronic and episodic migraine. Teva's acquisition of the LBR-101 program targeting high frequency episodic and chronic migraine complements the recent addition of Zecuity, an innovative therapy for the acute treatment of migraine, obtained through the acquisition of NuPathe.

This ability to treat both acute and chronic migraine builds on Teva's broader pain portfolio, which was recently further strengthened by positive phase III results achieved by Teva's potential abuse-deterrent extended release hydrocodone. The results gave a clear indication, in a clinical setting, of the promise of Teva's proprietary technology with potential abuse-deterrent properties in a range of opioid medications.

"Teva is the ideal company to continue Labrys' efforts to rapidly advance the LBR-101 program and bring a much needed product to market," said Steven P. James, Labrys' president and chief executive officer. "Since closing a Series A investment round in 2013, Labrys has made remarkable strides advancing LBR-101 in a robust phase 2 development program and attracting a high caliber company in Teva to complete clinical development."

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**International Microscopy Congress 2014.** Sep 12-14; Prague, Czech Republic; Web: www.imc2014.com

**MEMBS 2014 – 1st Middle East Molecular Biology Congress & Exhibition.** Sep 14-17; Dubai, UAE; Web: www.membs.org

**MipTec 2014.** Sep 23-25; Basel, Switzerland; Web: www.miptec.ch

## OCTOBER 2014

**31st World Congress of Biomedical Laboratory Sciences (IFBLS).** Oct 3-7; Taipei, Taiwan; Web: www.ifbls2014.org

**3rd EFLM-UEMS Congress, Laboratory Medicine at the Clinical Interface.** Oct 7-10; Liverpool, UK; Web: www.eurolabfocus2014.org

**JIB 2014 – Journées Internationales de Biologie.** Oct 8-10; Paris, France; Web: www.jib-sdbio.fr

**ECNP 2014 – 27th Congress of European College of Neuropsychopharmacology.** Oct 18-21; Berlin, Germany; Web: www.ecnp-congress.eu

**ESCMID – Conference on Redevelopment of Old Antibiotics.** Oct 20-24; Vienna, Austria; Web: www.escmid.org

**AACB 2014 – 52nd Annual Scientific Conference of the Australasian Association of Clinical Biochemists.** Oct 27-30; Adelaide, Australia; Web: www.aacb.asn.au

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**India Lab Expo 2014.** Nov 21-13; Hyderabad, India; Web: www.indialabexpo.com

**Association for Molecular Pathology (AMP) Annual Meeting 2014.** Nov 13-15; National Harbor, MD, USA; Web: www.amp.org

## DECEMBER 2014

**Annual ASCB Meeting – American Society for Cell Biology.** Dec 6-10; Philadelphia, PA, USA; Web: www.ascb.org

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**SLAS 2015 – Society of Laboratory Automation and Screening.** Feb 7-11; San Diego, CA, USA; Web: http://slas2015.org

**CHI 2015 – 21st International Molecular Medicine Tri-Conference.** Feb 15-20; San Francisco, CA, USA; Web: www.triconference.com

**Annual Meeting of the American Academy of Allergy, Asthma and Immunology.** Feb 20-24; Houston, TX, USA; Web: http://annualmeeting.aaaai.org

## MARCH 2015

**The Endocrine Society Annual Meeting.** Mar 5-8; San Diego, CA, USA; Web: www.endocrine.org

**PITTCON 2015 – Pittsburgh Conference on Analytical Chemistry and Applied Spectroscopy.** Mar 8-12; New Orleans, LA, USA; Web: http://pittcon.org

**Novel Drug Delivery Systems.** Mar 16-18; Dubai, UAE; Web: http://novel-drugdelivery-systems.pharmaceuticalconferences.com/

**Biotech World 2015.** Mar 17-20; Moscow, Russia; Web: www.mosbiotechworld.ru

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**ARAB LAB 2015.** Mar 23-26; Dubai, UAE; Web: www.arablab.com

**Experimental Biology 2015.** Mar 28-Apr 1; Boston, MA, USA; Web: http://experimentalbiology.org

**ASMB 2015 – Meeting for the American Society for Biochemistry & Molecular Biology.** Mar 28-Apr 1; Boston, MA, USA; Web: www.asbmb.org

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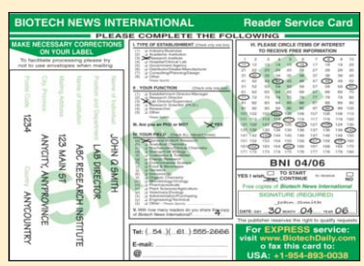

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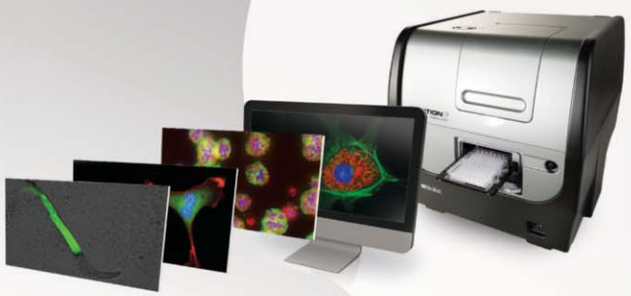

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