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Bio Research INTERNATIONAL

Blocking Growth Receptor for Nerve Regeneration

The mystery of why the human nervous system is unable to regenerate may have been at least partially solved with the identification of a protein called p75 that seems to block the repair of damaged nerve cells. Investigators at the Salk Institute for Biological Studies (La Jolla, CA, USA; www.salk.edu) explained

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X-Ray Powder Diffraction Technology Developed for Molecule Identification

A Danish researcher has developed a technique that uses X-rays for the rapid identification of substances present in an indeterminate powder. The new technique has the capacity to recognize sophisticated biologic molecules such as proteins. The method therefore has enormous potential in food production and the pharmaceutical industry, where it opens up, for example, new opportunities for the quality assurance (QA) of protein-based drugs. The technique was developed by a Technical University of Denmark (DTU; Kongens Lyngby; www.dtu.dk) researcher.

It is rarely sufficient to read the content information if one needs to

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Functional 3-D Brain-Like Tissue Model Bioengineered

Researchers reported on the development of the first complex, three-dimensional (3-D) model composed of brain-like cortical tissue that displays biochemical and electrophysiologic responses, and can function in the laboratory for months. The engineered tissue model offers new approaches for examining brain

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Nanoparticles to Deliver Drugs to Targeted Cells

Researchers have developed adaptable nanocarriers that can travel within the aqueous environment surrounding the cells and transport their passenger molecules through the membranes of such living cells in order to sequentially deliver their payloads.

See article on page 3

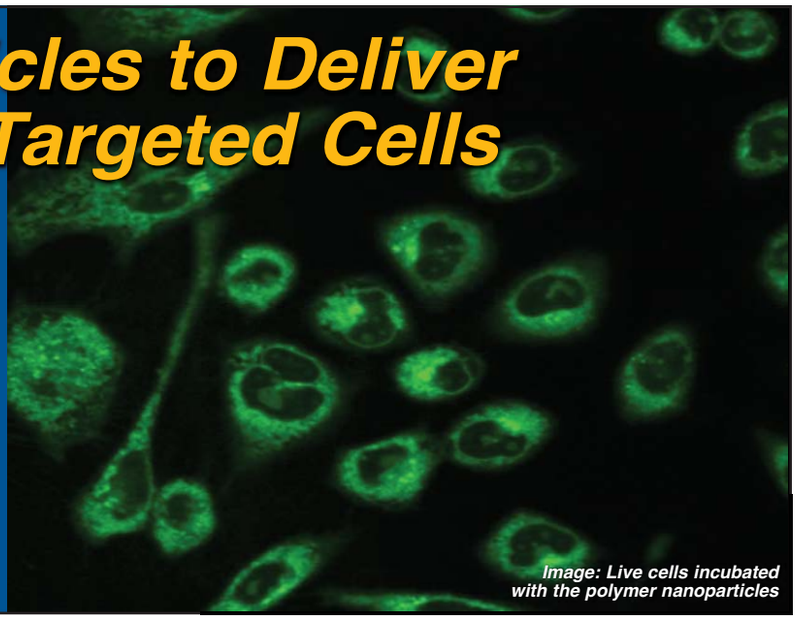

Image: Live cells incubated with the polymer nanoparticles

DNA Replication Difficulty Key to Immune System Aging

People over 60 are not donor candidates for bone marrow transplantation; the immune system ages and weakens with time, making the elderly predisposed to life-threatening infection and other disorders. US researchers have now have found a reason. "We have found the cellular mechanism responsible for the

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Inverted Microscope Designed to Readily Adapt to Changing Research Demands

A new inverted microscope for biotech and other life science laboratories was designed to readily accommodate modifications and upgrades to allow it to keep current with changing research demands and interests.

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Germany's Merck to Buy Sigma-Aldrich for USD 17 Billion

Merck KGaA will acquire Sigma-Aldrich for USD 17 billion, expanding its business in North America and gaining exposure in Asia. All outstanding shares of Sigma-Aldrich will be acquired by Merck for USD 140 per share, which would represent a 37% premium to Sigma-Aldrich's closing stock price of USD 102.37 on September 19, 2014. Merck anticipates achieving annual synergies of about EUR 260 million (~ USD 334 million) within three years after completion of the acquisition.

Karl-Ludwig Kley, chairman of Merck KGaA called the deal a "quantum

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INSIDE

Latest Advances & Applications in:

Image: No bigger than a soda can, the small-scale incubator microscope is a space-saving and cost-effective solution for time-lapse observation of cell cultures (Photo courtesy of Fraunhofer IBMT).

Small-Scale Incubator Microscope Designed to Study Cells in Time Lapse

German scientists have now devised innovative technology that combines the functions of both incubators and microscopes in a compact small-scale system. It is ideally suited for time-lapse study over a number of weeks and for automatic observation of cell cultures. The incubator microscope is no bigger than a soda can, and costs 30 times less than purchasing an incubator and a microscope separately.

Similar to humans, cells require nutrients to survive. Cultivating human and animal cells requires parameters such as temperature and humidity to be specified with absolute precision and maintained at an even level over long periods of time. Time-lapse observation over a period of some weeks can be particularly beneficial, since a lot occurs in that time in terms of cell reproduction and differentiation. Until now, the typical way to make these sorts of observations has been to use small incubators in combination with traditional microscopes. This takes up about one square meter of space, making operating several such systems alongside each other an inefficient process. There is a need for innovative solutions that will substantially reduce the space needed and the costs involved without compromising the quality of the cultivation and of the microscope images recorded.

The small-scale incubator microscope system can be used for time-lapse observation of cell cultures as well as to collect fluorescent images at different wavelengths. It includes a small incubation chamber and control electronics to provide defined cell culture parameters. Cells grow on the floor of the miniaturized incubation chamber on a thin, replaceable glass plate and are supplied with a constant stream of nutrients. The only parameters that need to be kept constant within the incubator are the temperature and the nutrient supply flow rate. The small-scale incubator microscope allows for many units to be operated in parallel in a very compact space. Moreover, in spite of its space-saving design, the system generates images that are almost as good as those of the bigger microscopes.

Prototype versions are now in use in a range of research projects. "The system is stable and can be used for time-lapse observation spanning several weeks," commented Dr. Thomas Velten, head of the biomedical microsystems department at the Fraunhofer Institute for Biomedical Engineering IBMT (Berlin, Germany; www.researchgate.net). The device continuously gathers data and saves it to a computer. Images can be accessed at any time and analyzed using the appropriate image processing software.

"Our customers get a biomedical analysis tool of the highest quality – well priced, space-saving, and tailored to their needs," concluded Dr. Velten. The incubator microscope is suited to a wide variety of applications, for instance examining the reaction of cells to nanoparticles or toxic agents in the environment. Another current application is stem cell research. "The system is compact, mobile, extremely efficient, and fully automatic in operation."

Nanoparticles to Deliver Drugs to Targeted Cells

Investigators are exploring the use and behavior of nanoparticles to deliver molecules to target cells. There is a great demand for the development of nanoparticles that can transport and deliver drugs to target cells in the human body. Researchers from the University of Miami (UM; Coral Gables, USA; www.miami.edu) have created nanoparticles that, under favorable settings, can self-assemble, ensnaring complementary guest molecules within their structure. These adaptable nanocarriers can travel in the aqueous environment encircling cells and transport their passenger molecules through the membrane of living cells to sequentially deliver their payload.

Although the transport of molecules inside cells with nanoparticles has been earlier achieved using various methods, researchers have developed nanoparticles capable of delivering and exchanging complementary molecules. For practical applications, these nanocarriers are highly desirable, reported Francisco Raymo, professor of chemistry in the University of Miami College of Arts and Sciences and lead investigator of the project. "The ability to deliver distinct species inside cells independently and force them to interact, exclusively in the intracellular environment, can evolve into a valuable strategy to activate drugs inside cells," said Prof. Raymo.

The new nanocarriers are 15 nm in diameter. They are supramolecular constructs comprised of amphiphilic polymers. These nanocarriers hold the guest molecules within the boundaries of their water-insoluble core and use their water-soluble exterior to move through an aqueous environment. As a result, these nanovehicles are is suitable for transferring molecules, which would otherwise be insoluble in water, across a liquid environment.

"Once inside a living cell, the particles mix and exchange their cargo. This interaction enables the energy transfer between the internalized molecules," said Prof. Raymo, director of UM's laboratory for molecular photonics. "If the complementary energy donors and acceptors are loaded separately and sequentially, the transfer of energy between them occurs exclusively within the intracellular space. As the energy transfer takes place, the acceptors emit a fluorescent signal that can be observed with a microscope."

Crucial for this process are the noncovalent bonds that loosely hold the supramolecular constructs together. These weak bonds exist between molecules with complementary shapes and electronic characteristics. They are responsible for the ability of supramolecules to assemble spontaneously in liquid environments. Under the right conditions, the reversibility of these weak noncovalent contacts allows the supramolecular constructs to exchange their components as well as their cargo.

The research was conducted with cell cultures. It is not yet known if the nanoparticles can actually travel through the bloodstream. "That would be the dream, but we have no evidence that they can actually do so," said Prof. Raymo. "However, this is the direction we are heading."

The next step of this study involves demonstrating that this method can be used to do chemical reactions inside cells, instead of energy transfers. "The size of these nanoparticles, their dynamic character, and the fact that the reactions take place under normal biological conditions [at ambient temperature and neutral environment] makes these nanoparticles an ideal vehicle for the controlled activation of therapeutics directly inside the cells," Prof. Raymo concluded.

The study's findings were published in the *Journal of the American Chemical Society*.

Loss of Endothelial Cell Enzyme Restores Sensitivity to Chemotherapy And Radiation in Nearby Tumor Cells

Cancer researchers have found that an enzyme produced by cells in the blood vessels that serve tumors triggers the release of signaling molecules that stimulate the repair of damage to the tumor cells caused by treatment with radiation or chemotherapeutic agents.

Investigators at Queen Mary University (London, United Kingdom; www.qmul.ac.uk) examined the role of the enzyme focal adhesion kinase (FAK) in noncancerous endothelial cells in regions of tumor growth.

FAK is a 125-kDa protein that is known to participate in focal adhesion dynamics between cells with a role in motility and cell survival. FAK is a highly conserved, nonreceptor tyrosine kinase originally identified as a substrate for the oncogene protein, tyrosine kinase v-src. This cytoplasmic kinase has been implicated in diverse cellular roles including cell locomotion, mitogen response, and cell survival. FAK is typically located at structures known as focal adhesions, which are multiprotein structures that link the extracellular matrix (ECM) to the cytoplasmic cytoskeleton. It has been shown that when FAK was blocked, breast cancer cells became less metastatic due to decreased mobility.

In the current study, the investigators blocked FAK activity in the cells lining blood vessels in a mouse tumor model. They found that deletion of FAK in endothelial cells had no apparent effect on blood vessel function but induced increased apoptosis and decreased proliferation of tumor cells in doxorubicin- and radiotherapy-treated mice. Mechanistically, they demonstrated that endothelial-cell FAK was required for DNA-damage-induced NF-kappaB activation in vivo and in vitro and for the production of cytokines from endothelial cells. Loss of endothelial-cell FAK reduced DNA-damage-induced cytokine production, thus enhancing chemosensitization of tumor cells to DNA-damaging therapies in vitro and in vivo.

Additional data published in the July 27, 2014, online edition of the journal *Nature* revealed that that low blood vessel FAK expression was associated with complete remission in human lymphoma.

First author Dr. Bernardo Tavora, a postdoctoral associate at Queen Mary University, said, "This work shows that sensitivity to cancer treatment is related to our own body mistakenly trying to shield the cancer from cell-killing effects caused by radiotherapy and chemotherapy. Although taking out FAK from blood vessels will not destroy the cancer by itself, it can remove the barrier cancer uses to protect itself from treatment."

CT Scan Casts Doubt on Hominid Child's Brain Development Is Similar to That of Modern Humans

By undergoing advanced computed tomography (CT) scanning, the skull of the famous fossil child is providing evidence for researchers against the human evolutionary hypotheses that the hominid *Australopithecus africanus* shows the same cranial adaptations found in modern human infants and toddlers. The Taung Child, South Africa's most important hominid fossil remains discovered 90 years ago by Wits University Prof. Raymond Dart, is providing major insights into human origins. By subjecting the skull of the first australopith discovered to the latest technologies in the University of the Witwatersrand Microfocus X-ray Computed Tomography (Johannesburg, South Africa; www.wits.ac.za) facility, researchers are refuting current backing for the hypothesis that this early hominid exhibits infant brain development in the prefrontal region similar to that of modern humans.

The findings have been published online on August 25, 2014, in the *Proceedings of the National Academy of Sciences of the United States of America (PNAS)*. The Taung Child has historic and scientific significance in the fossil record as the first and best instance of early hominid brain evolution, and theories have been presented that it offers key cranial adaptations seen in modern human infants and toddlers.

To assess the precise age of this evolutionary adaptation, Dr. Kristian J. Carlson, senior researcher from the Evolutionary Studies Institute at the University of the Witwatersrand, and colleagues, Prof. Ralph L. Holloway from Columbia University (New York, NY, USA; www.columbia.edu) and Douglas C. Broadfield from Florida Atlantic University (Boca Raton, USA; www.fau.edu), performed an in silico dissection of the Taung fossil using high-resolution CT imaging.

"A recent study has described the roughly three million-year-old fossil, thought to have belonged to a three- to four-year-old, as having a persistent metopic suture and open anterior fontanelle, two features that facilitate post-natal brain growth in human infants when their disappearance is delayed," said Dr. Carlson.

Comparisons with the existing hominid fossil record and chimpanzee variation do not support this evolutionary scenario. Mentioning flaws in how the Taung fossil material has been recently assessed, the researchers suggest physical evidence does not incontrovertibly link characteristics of the Taung skull, or its endocast, to early prefrontal lobe expansion, a brain region associated with many human behaviors.

The scientists also argued against the earlier proposed theoretical foundation for this adaptation in *A. africanus*. By refuting the presence of these features in the Taung Child, the researchers dispute whether these structures were selectively beneficial in hominid evolution, especially in australopith hominids.

Therefore, study's findings revealed that there is still no evidence for this sort of skull adaptation that evolved before modern man, neither is there evidence for a link between such skull characteristics and the suggested accompanying early prefrontal lobe expansion, according to Dr. Carlson.

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Yerel süreli yayındır, iki ayda bir yayınlanır, ücretsiz dağıtılır.

X-Ray Powder Diffraction Technology Developed for Molecule Identification

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know exactly what substances a product contains. One needs to be a very skilled chemist or to have "X-ray vision" to look directly into the molecular structure of the various substances. Christian Grundahl Frankaer, a postdoc in the DTU department of chemical engineering, is almost both, as he has developed technology that allows him to use X-rays to look deep into biologic samples.

The technique is called powder diffraction and involves subjecting a sample to an intense beam of X-rays. When the beam hits the sample, it disseminates in the same manner as light does when reflected by a disco ball. This generates a pattern that reflects the structure of the substance. Each individual substance has its own unique pattern, which makes it easily identifiable when the findings are run through a database.

Powder diffraction is currently used to identify basic substances such as salts, sugars, and minerals, but the theory behind using the same technique to characterize complicated biologic molecules such as proteins is groundbreaking. It is for this reason that the technology has huge possibilities in both food production and the pharmaceutical industry, where more and more attention is being dedicated to protein-based medicines.

Image: The new method makes it possible to establish very quickly what substances – proteins and others – a product in powder form contains. For example, a quick analysis of a washing powder developed for the Danish market revealed a high level of zeolite material, which is used to bind limestone from the hard water that is so prevalent in Denmark, while a sample from Morocco contained none of this material. Analysis of another washing powder revealed that "active oxygen" is simply the compound sodium percarbonate, i.e., bonded hydrogen peroxide (Photo courtesy of Iben Julie Schmidt / Technical University of Denmark).

"I have tested different types of infant milk formula, protein powders and detergents. By taking a small sample of powder and bombarding it with X-rays, I can determine what substances the powder contains, and in what concentrations, within 10 minutes. In addition, the analysis will typically reveal some information about how the product was made," noted Dr. Frankaer. The method is therefore perfect for quality assurance of new products on the market.

Dr. Franaer added, "We have now demonstrated that powder diffraction can actually be used on biological substances such as proteins. The results are not as detailed as in single crystal diffraction, which makes it possible to decode the entire structure of the protein, but they do allow us to 'lift fingerprints' quickly and easily so that we can identify the protein and its crystal structure. This is valuable knowledge when you are working with the production of proteins."

The technology has great potential in the framework of optimizing both quality and production processes in all production set-ups that involve solid substances. Applying the new approach will make it possible to check continuously for alterations in – or transformations of – different materials used in the production process. "The advantage of our method is that it allows you to take samples directly from a production line. You then have the results within 15 minutes and can tell precisely what crystalline material is involved. In addition, the X-ray beams we use can easily be generated using standard laboratory equipment," stated Dr. Frankaer.

The promising findings are just beginning of the project, "What we want to do now is to test how far we can push the method. We have already established that it works on proteins, but will it also work on other complex products? And what happens if we take the samples to the synchrotron in Grenoble [France], where the X-ray beam is a million times more powerful than the one we have in our laboratory?" queried Dr. Frankaer.

Crystal Structures Define Mode of Action of Bacteriophage Endolysins

New antibacterial agents based on bacteriophages or their endolysin enzymes have been proposed to solve the problem of the bacterium *Clostridium difficile*, which is becoming a serious health hazard in hospitals and healthcare institutes, due to its resistance to antibiotics.

Investigators at the European Molecular Biology Laboratory (Hamburg, Germany; www.embl.de) based their research primarily on the bacteriophage CD27, which is capable of lysing *C. difficile*. In addition, they worked with a recombinant form of the CD27L endolysin, which lyses *C. difficile* in vitro.

To better understand how the lysis process works, the investigators determined the three-dimensional structures of the CD27L endolysin and the CTP1L endolysin from the closely related bacteriophage CPT1 that targets *C. tyrobutyricum*. For this task they employed X-ray crystallography and small angle X-ray scattering (SAXS), which was done at the Deutsches Elektronen-Synchrotron (DESY).

Results published in the July 24, 2014, online edition of the journal *PLOS Pathogens* revealed that the two endolysins shared a common activation mechanism, despite having been taken from different species of *Clostridium*. The activation mechanism depended on a structure where an extended dimer existed in the inactive state but switched to a side-by-side "relaxed" morphology in the active state, which triggered the cleavage of the C-terminal domain. This change of morphology led to the release of the catalytic portion of the endolysin, enabling the efficient digestion of the bacterial cell wall.

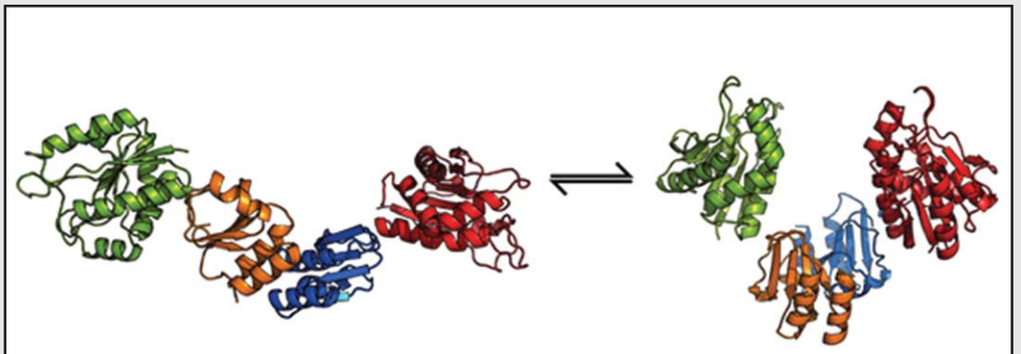

Image: The viral endolysins are activated by switching from a tensed, stretched state (left) to a relaxed state (right) (Photo courtesy of EMBL / Rob Meijers).

"These enzymes appear to switch from a tense, elongated shape, where a pair of endolysins is joined together, to a relaxed state where the two endolysins lie side-by-side," said first author Dr. Matthew Dunne, a researcher at the European Molecular Biology Laboratory. "The switch from one conformation to the other releases the active enzyme, which then begins to degrade the cell wall."

Functional 3-D Brain-Like Tissue Model Bioengineered

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function, disease, and trauma, and treatment. The US National Institutes of Health (NIH; Bethesda, MD, USA)-funded study findings were published in the August 11, 2014, of the *Proceedings of the National Academy of Sciences of the United States of America (PNAS)*. Furthering the study of brain trauma, disease, and therapeutic treatments is something that the study's senior and corresponding author, David Kaplan, PhD, is a professor and chair of biomedical engineering at Tufts School of Engineering (Medford/Somerville, MA, USA; http://engineering.tufts.edu), has wanted to pursue for quite a while.

The human brain remains one of the least understood organs in the human body, because of its complexity and the difficulty of studying its physiology in the living body. "There are few good options for studying the physiology of the living brain, yet this is perhaps one of the biggest areas of unmet clinical need when you consider the need for new options to understand and treat a wide range of neurological disorders associated with the brain. To generate this system that has such great value is very exciting for our team," said Dr. Kaplan, who directs the NIH-funded P41 Tissue Engineering Resource Center based at Tufts.

Instead of rebuilding a whole-brain network, the Tufts scientists generated a modular design that replicated basic features most pertinent to the brain's tissue-level physiologic functions. Each module merged two substances with diverse characteristics: a stiffer porous scaffold comprised of cast silk protein on which the cortical neurons, derived from rats, could anchor and a softer collagen gel matrix that allowed axons to penetrate and connect in a three dimensional (3-D) way. Circular modules of cast silk were punched into doughnuts, and then assembled into concentric rings to simulate the laminal layers of the neocortex. Each layer was seeded with neurons independently before assembly, without the need for adhesive or glue. The doughnuts were then immersed in the collagen gel matrix.

The silk-collagen gel combo provided an ideal microenvironment for neural network formation and function. "The stiffness of the silk biomaterial could be tuned to accommodate the cortical neurons and the different types of gels, maintaining both stability in culture and brain-like tissue elasticity," said the study's first author, Min D. Tang-Schomer, PhD, postdoctoral scholar in biomedical engineering at Tufts. "The tissue maintained viability for at least nine weeks – significantly longer than cultures made of collagen or hydrogel alone – and also offered structural support for network connectivity that is crucial for brain activity."

The Tufts researchers were able to use the tissue model to examine multiple post-injury effects, including cellular damage, neurochemical changes, and electrophysiological activity. For example, when a weight was dropped on the model tissue to simulate a traumatic brain injury, the tissue released high levels of the chemical glutamate, a neurotransmitter known to be emitted by cells following brain damage; the tissue also showed transient electrical hyperactivity consistent with post-trauma responses observed in vivo.

"This model provides a unique opportunity for mapping out real-time neurophysiological events and function-studies in the laboratory, monitoring that is prohibitive with humans or animals," said study coauthor Philip Haydon, PhD, a professor of neuroscience at the Sackler School of Graduate Biomedical Sciences, Tufts University School of Medicine.

According to Dr. Kaplan, this research is underway to additionally engineer the model. It could potentially be applied to study brain structure-function, drug screening, impact of electrodes and implants on brain function, disease formation and treatments, and the effects of nutrition and toxicants. "This is the first step," he emphasized.

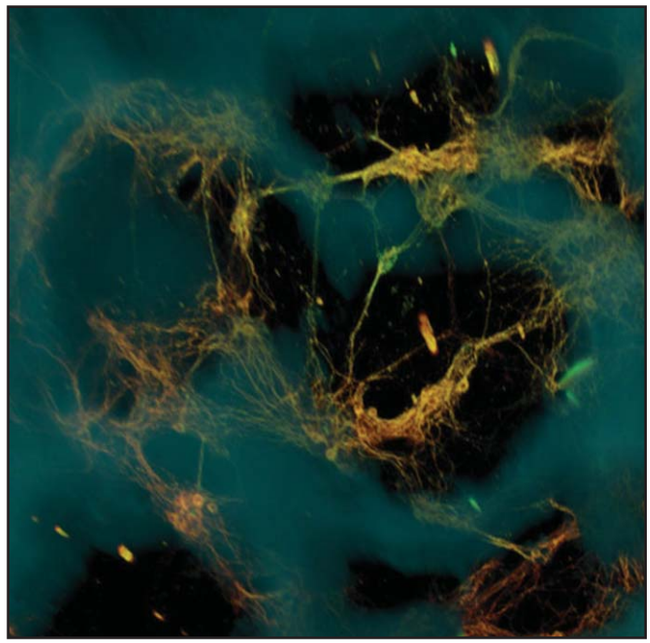


Image: Bioengineers have created three-dimensional brain-like tissue that functions like and has structural features similar to tissue in the rat brain. The neurons formed functional networks throughout the scaffold pores (dark areas) (Photo courtesy of Tufts University).

Compact Ultra-Low-Temperature Storage Solutions Available

A line of advanced deep freezers with robotic sample access is now available for biotech and life science laboratories. The Hamilton Storage Technologies (Franklin, MA, USA; www.hamilton-storage.com) BiOS M and L are two compact high-density systems for the ultra-low-temperature storage of sensitive biological samples.

All samples within the BiOS systems are stored in -80 degrees Celsius chest freezer compartments to maintain temperature stability. All internal workflows, including sample picking, are optimized to keep samples at ultra-low temperatures at all times. System parts are easily accessible for service and maintenance, while one-dimensional and two-dimensional barcode reading and sample tracking provide complete chain-of-custody documentation – a requirement for forensic laboratories. Multiple backup systems ensure that samples stay at -80 degrees Celsius in the event of power failure.

"By adding smaller configurations of our high-capacity BiOS -80 degree Celsius storage system, more labs have access to state-of-the-art sample storage within steps of their sample preparation and analysis stations," said Dr. Martin Frey, PhD, head of Hamilton Storage Technologies. "This reduces the likelihood that results may be compromised."

Image: The Hamilton BiOS M, designed for ultra-low-temperature storage of sensitive biological samples (Photo courtesy of Hamilton Storage Technologies).

Rainbow Mouse Model Reveals Secrets of Kidney Regeneration

The ability of the kidney to regenerate following disease or injury has been linked to the activation of the WNT signaling pathway and the generation of segment-specific fate-restricted clones. How the mammalian kidney generates and maintains its proximal tubules, distal tubules, and collecting ducts has been a controversial topic for researchers in this field. In the current study, investigators at Tel Aviv University (Israel; www.tau.ac.il) and colleagues at Stanford University (Palo Alto, CA, USA; www.stanford.edu) employed the novel "rainbow mouse" model to investigate kidney regeneration at the cellular level.

The rainbow mouse is a line that was genetically engineered to express one of four alternative fluorescent reporters in each cell. These markers enabled tracing cell growth in vivo. Working with the rainbow mouse model, the investigators employed long-term in vivo genetic lineage tracing and clonal analysis of individual cells from kidneys undergoing development, maintenance, and regeneration.

The investigators reported in the May 22, 2014, issue of the journal *Cell Reports* that the adult mammalian kidney underwent continuous synthesis of tubules via expansions of fate-restricted clones. Kidneys recovering from damage maintained tubule synthesis through expansions of clones with segment-specific borders. Renal spheres developing in vitro from individual cells retained distinct, segment-specific fates.

Analysis of mice derived by transfer of color-marked embryonic stem cells (ESCs) into uncolored blastocysts demonstrated that nephrons were polyclonal, developing from expansions of singly fated clones. Adult renal clones were derived from Wnt-responsive precursors, and their tracing in vivo generated tubules that were segment specific.

Wnt signaling molecules regulate cell-to-cell interactions during embryogenesis. Wnt genes and Wnt signaling are also implicated in cancer. Although the presence and strength of any given effect depends on the WNT ligand, cell type, and organism, some components of the signaling pathway are remarkably conserved in a wide variety of organisms.

"Our aim was to use a new technique to analyze an old problem," said senior author Dr. Benjamin Dekel, professor of pediatrics at Tel Aviv University." No one had ever used a rainbow mouse model to monitor development of kidney cells. It was exciting to use these genetic tricks to discover that cellular growth was occurring all the time in the kidney – that, in fact, the kidney was constantly remodeling itself in a very specific mode. We were amazed to find that renal growth does not depend on a single stem cell, but is rather compartmentalized. Each part of the nephron is responsible for its own growth, each segment responsible for its own development, like a tree trunk and branches – each branch grows at a different pace and in a different direction. This study teaches us that in order to regenerate the entire kidney segments different precursor cells grown outside of our bodies will have to be employed. In addition, if we were able to further activate the WNT pathway, then in cases of disease or trauma we could activate the phenomena for growth and really boost kidney regeneration to help patients. This is a platform for the development of new therapeutics, allowing us to follow the growth and expansion of cells following treatment."

"We wanted to change the way people thought about kidneys – about internal organs altogether," said Dr. Dekel. "Very little is known even now about the way our internal organs function at the single cell level. This study flips the paradigm that kidney cells are static – in fact, kidney cells are continuously growing, all the time."

Brain Scanner Shows Infants' Brains Rehearse Speech Sounds Months Before Their First Words

New research in 7- and 11-month-old infants revealed that speech sounds stimulate brain regions that coordinate and plan motor movements for speech. The new study suggests that babies' brains begin establishing the foundation of how to form words long before they actually begin to speak and this may affect the developmental transition.

Infants notice the difference between sounds of all languages until about eight months of age when their brains begin to concentrate only on the sounds they hear around them. It is not known how this transition occurs, but social interactions and caregivers' use of embellished "parentese" manner of speech appear to help.

The study's findings were published July 14, 2014, in the *Proceedings of the National Academy of Sciences of the United States of America (PNAS)*. "Most babies babble by seven months, but don't utter their first words until after their first birthdays," said lead author Dr. Patricia Kuhl, who is the co-director of the University of Washington's (UW; Seattle, USA; www.washington.edu) Institute for Learning and Brain Sciences. "Finding activation in motor areas of the brain when infants are simply listening is significant, because it means the baby brain is engaged in trying to talk back right from the start and suggests that seven-month-olds' brains are already trying to figure out how to make the right movements that will produce words."

Dr. Kuhl and her research colleagues think this practice at motor planning contributes to the transition when babies become more sensitive to their native language. These findings stress the importance of talking to kids during social interactions even if they are not talking back yet. "Hearing us talk exercises the action areas of infants' brains, going beyond what we thought happens when we talk to them," Dr. Kuhl said. "Infants' brains are preparing them to act on the world by practicing how to speak before they actually say a word."

In the research, infants sat in a brain scanner that measures brain activation through a noninvasive technique called magnetoencephalography (MEG). The brain scanner resembles an egg-shaped old-fashioned hair dryer and is completely safe for infants. The Institute for Learning and Brain Sciences was the first in the world to use such a tool to study babies while they engaged in a task.

Each of the infants, 57 7- and 11- or 12-month-olds, listened to a series of native and foreign language syllables such as "da" and "ta" as researchers recorded brain responses. They listened to sounds in English and in Spanish. The researchers examined brain activity in an auditory area of the brain called the superior temporal gyrus, as well as in Broca's area and the cerebellum, cortical regions responsible for planning the motor movements required for producing speech.

This pattern of brain activation occurred for sounds in the seven-month-olds' native language (English) as well as in a non-native language (Spanish), showing that at this early age infants are responding to all speech sounds, whether or not they have heard the sounds before.

In the older infants, brain activation was different. By 11-12 months, babies' brains increase motor activation to the non-native speech sounds comparative to their native speech, which the researchers interpret as showing that it takes more effort for the baby brain to forecast which movements create non-native speech. This reflects an effect of experience between 7 and 11 months, and suggests that activation in motor brain areas is contributing to the transition in early speech perception.

The study has social implications, suggesting that the slow and exaggerated-style of parentese speech – "Hiiiii! How are youuuuu?" – may actually prompt infants to try to synthesize utterances themselves and imitate what they heard, uttering something like "Ahhh bah bah baaah."

"Parentese is very exaggerated, and when infants hear it, their brains may find it easier to model the motor movements necessary to speak," Dr. Kuhl said.

Image: A one-year-old baby sits in a brain scanner, called magnetoencephalography – a noninvasive approach to measuring brain activity. The baby listens to speech sounds like "da" and "ta" played over headphones while researchers record her brain responses (Photo courtesy of the Institute for Learning & Brain Sciences, UW).

Factors in the Tumor Microenvironment Promote Cancer Growth and Metastasis

Cancer researchers have found that procancerous HSF1 (Heat shock factor 1) drives a transcriptional program in cancer-associated fibroblasts (CAFs) that complements, yet is completely different from, the program it drives in adjacent cancer cells.

Stromal cells within the tumor microenvironment are essential for tumor progression and metastasis, but little is known about the factors that drive the transcriptional reprogramming of stromal cells within tumors. Investigators at the Whitehead Institute for Biomedical Research (Cambridge, MA, USA; www.wi.mit.edu) recently reported that the transcriptional regulator heat shock factor 1 (HSF1) was frequently activated in cancer-associated fibroblasts (CAFs), where it was a potent enabler of malignancy. HSF1 activity was found in a variety of human tumors, including breast, lung, skin, esophageal, colon, and prostate cancers.

HSF1 is the major regulator of heat shock protein transcription in eukaryotes. In the absence of cellular stress, HSF1 is inhibited by association with the heat shock proteins Hsp40/Hsp70 and Hsp90 and is therefore not active. Cellular stresses, such as increased temperature, can cause misfolding of proteins in the cell. Heat shock proteins bind to the misfolded proteins and dissociate from HSF1. This allows HSF1 to form trimers and translocate to the cell nucleus where it is hyperphosphorylated, binds to DNA containing heat shock elements, and activates transcription.

The investigators reported in the July 31, 2014, issue of the journal *Cell* that analysis of tumor samples from breast cancer and non-small-cell lung cancer patients revealed that HSF1 activation in the stroma was associated with poor patient outcomes, including reduced disease-free survival and overall survival. Thus, stromal HSF1 is considered to be a possible biomarker for cancer diagnosis and prognosis as well as a potential drug target.

"This is actually a beautiful example of evolution," said Dr. Ruth Scherz-Shouval, a postdoctoral researcher at the Whitehead Institute for Biomedical Research. "It is recognizing that the tumor is like an organism that adheres to evolutionary principles. HSF1 has been highly conserved over time, supporting the survival of organisms ranging from yeast to human, so it makes sense that it is coopted here. Both cancer cells and the microenvironment are sensing changes in the tumor and responding, signaling to one another to help the "organism," albeit to the detriment of the host. These are different programs, but they are both controlled by HSF1 and serve the same purpose."

"It is important to find HSF1 operating this way in the stroma," said Dr. Scherz-Shouval. "The tumor microenvironment tends to be more genetically stable and less prone to mutation, suggesting that even if cancer cells could mutate to evade therapeutic disruption of HSF1, supportive cells in the stroma could still be susceptible."

Experimental Drug Slows Progress Of Parkinson's in Rat Model

In a series of experiments designed to set the stage for future human clinical trials, an experimental anti-inflammatory drug was shown to prevent loss of dopamine-producing neurons and to reduce motor deficits in a rat model of Parkinson's disease (PD).

Investigators at Emory University (Atlanta, GA, USA; www.emory.edu) had demonstrated previously that selective inhibition of soluble Tumor Necrosis Factor (solTNF) by injection into the brain (intranigral delivery) of dominant negative TNF (DN-TNF) inhibitors reduced neuroinflammation and nigral dopamine (DA) neuron loss in endotoxin and neurotoxin rat models of PD.

In the current study, they used a rat PD model in which the human disease was mimicked by injection of the animals in one side of the brain with the neurotoxin 6-hydroxydopamine (6-OHDA). The resulting syndrome reflected certain aspects of human PD: dopamine-producing neurons in the injected side of the brain died, leading to impaired movement on the opposite side of the body. The investigators sought to determine whether peripherally administered DN-TNF inhibitor XPro1595 could cross the blood-brain-barrier in therapeutically relevant concentrations and whether the drug would attenuate neuroinflammation and prevent loss of dopamine-producing neurons.

Xpro1595, which was developed by FPRT Bio (Scranton, PA, USA; http://fprtbio.com), is a novel protein therapeutic agent that neutralizes soluble TNF (sTNF) using Dominant-Negative TNF technology. The mode of operation of the drug is very simple, yet very elegant. Human sTNF exists as three identical monomers that bind neatly into the TNF receptor (TNFR). The binding of normal sTNF to the TNFR is required for the biologic effect. Xpro1595 is an engineered protein that has six amino acid substitutions that makes it slightly different from normal human sTNF. XPro1595 can freely bind with normal monomers to form heterotrimers, but the heterotrimers cannot bind to TNFR. This eliminates any biologic effects of the sTNF. Thus, XPro1595 completely and efficiently neutralizes sTNF. This is a unique biologic property of XPro1595 that has important therapeutic implications.

Results published in the July 24, 2014, online edition of the *Journal of Parkinson's Disease* revealed that XPro1595 could reach the brain at sufficient levels to have beneficial effects when administered by subcutaneous injection. Rats dosed with XPro1595 three days after 6-OHDA injection lost only 15% of dopamine-producing neurons as compared to controls that lost 55% of the same neurons. Animals treated with XPro1595 two weeks after 6-OHDA injection lost 44% percent of dopamine-producing neurons, suggesting that there was a limited time frame for effective use of the drug.

"Recent clinical studies indicated there is a four or five year window between diagnosis of Parkinson's disease and the time when the maximum number of vulnerable neurons are lost," said senior author Dr. Malu Tansey, associate professor of physiology at Emory University. "If this is true, and if inflammation is playing a key role during this window, then we might be able to slow or halt the progression of Parkinson's with a treatment like XPro1595."

"This is an important step forward for anti-inflammatory therapies for Parkinson's disease," said Dr.Tansey. "Our results provide a compelling rationale for moving toward a clinical trial in early Parkinson's disease patients. Inflammation is probably not the initiating event in Parkinson's disease, but it is important for the neurodegeneration that follows. That is why we believe that an anti-inflammatory agent, such as one that counteracts soluble TNF, could substantially slow the progression of the disease."

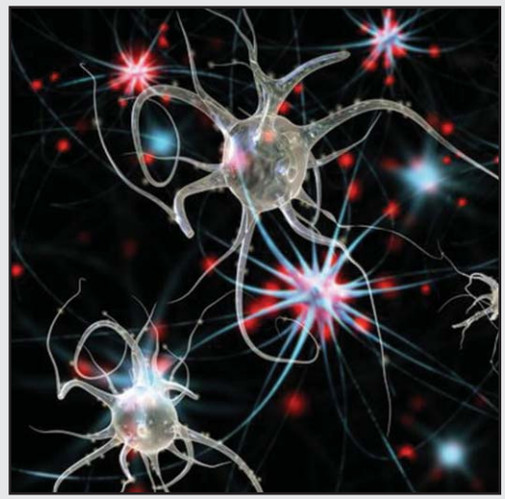
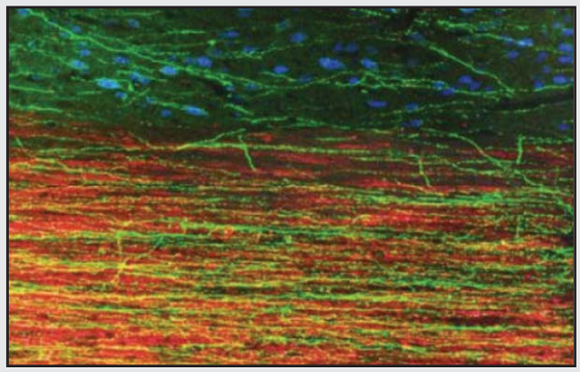


Image: Researchers may be one step closer to stopping early progression of Parkinson's disease by targeting the inflammation that kills neurons (Photo courtesy of Shutterstock).

Grafted Human Stem Cells Experience Drastic Growth in Spinal Cords of Rats



Scientists have reported that neurons derived from human induced pluripotent stem cells (iPSCs) and grafted into rats after a spinal cord injury produced cells with tens of thousands of axons extending virtually the entire length of the animals' central nervous system (CNS).

Drawing upon earlier studies, scientists from the University of California (UC), San Diego School of Medicine (USA; http://med.ucsd.edu) and Veteran's Affairs San Diego Healthcare System reported that neurons derived from iPSCs and grafted into lab rats after a spinal cord injury generated cells with tens of thousands of axons extending virtually the entire length of the rodents' CNS.

Writing in the August 7, 2014, early online edition of the journal *Neuron*, lead scientist Paul Lu, PhD, of the UC San Diego department of neurosciences and colleagues reported that the human iPSC-derived axons extended through the white matter of the injury sites, frequently penetrating adjacent gray matter to form synapses with rat neurons. Similarly, rat motor axons penetrated the human iPSC grafts to form their own synapses.

The iPSCs used were developed from a healthy 86-year-old human male. "These findings indicate that intrinsic neuronal mechanisms readily overcome the barriers created by a spinal cord injury to extend many axons over very long distances, and that these capabilities persist even in neurons reprogrammed from very aged human cells," said senior author Mark Tuszynski, MD, PhD, professor of neurosciences and director of the UC San Diego Center for Neural Repair.

For several years, Dr. Tuszynski and colleagues have been steadily chipping away at the notion that a spinal cord injury necessarily results in permanent dysfunction and paralysis. Earlier work has shown that grafted stem cells reprogrammed to become neurons can, in fact, form new, functional circuits across an injury site, with the treated animals experiencing some restored capability to move affected limbs. The new findings emphasize the potential of iPSC-based therapy and suggest a range of new studies and problems to be solved, such as whether axons can be guided and how will they develop, function and mature over longer periods of time.

While neural stem cell therapies are already advancing to clinical trials, this research raises cautionary notes about moving to human therapy too quickly, according to Dr. Tuszynski. "The enormous outgrowth of axons to many regions of the spinal cord and even deeply into the brain raises questions of possible harmful side effects if axons are mistargeted. We also need to learn if the new connections formed by axons are stable over time, and if implanted human neural stem cells are maturing on a human time frame – months to years – or more rapidly. If maturity is reached on a human time frame, it could take months to years to observe functional benefits or problems in human clinical trials."

In the latest research, Drs. Lu, Tuszynski and colleagues converted skin cells from a healthy 86-year-old man into iPSCs. The iPSCs were then reprogrammed to become neurons in collaboration with the laboratory of Larry Goldstein, PhD, director of the UC San Diego Sanford Stem Cell Clinical Center. The new human neurons were then embedded in a matrix containing growth factors and grafted into two-week-old spinal cord injuries in rats.

Three months later, researchers examined the post-transplantation injury sites. They found biomarkers indicating the presence of mature neurons and extensive axonal growth across long distances in the animals' spinal cords, even extending into the brain. The axons traversed wound tissues to penetrate and connect with existing rat neurons. Correspondingly, rat neurons extended axons into the grafted material and cells. The transplants produced no identifiable tumors.

Even though numerous connections were formed between the implanted human cells and rat cells, functional recovery was not found. However, Dr. Lu noted that tests evaluated the rats' skilled use of the hand. Simpler assays of leg movement could still show benefit. Moreover, several iPSC grafts contained scars that may have suppressed beneficial effects of new connections. Continuing research will help to optimize transplantation techniques to eliminate scar formation.

According to Dr. Tuszynski, he and his team are trying to identify the most promising neural stem cell type for repairing spinal cord injuries. They are examining iPSCs, embryonic stem cell-derived cells, and other stem cell types. "Ninety-five percent of human clinical trials fail. We are trying to do as much as we possibly can to identify the best way of translating neural stem cell therapies for spinal cord injury to patients. It's easy to forge ahead with incomplete information, but the risk of doing so is greater likelihood of another failed clinical trial. We want to determine as best we can the optimal cell type and best method for human translation so that we can move ahead rationally and, with some luck, successfully."

Image: An extension of human axons into host adult rat white matter and gray matter three months after spinal cord injury and transplantation of human induced pluripotent stem cell-derived neurons. Green fluorescent protein identifies human graft-derived axons, myelin (red) indicates host rat spinal cord white matter and blue marks host rat gray matter (Photo courtesy of the UC San Diego School of Medicine).

Leukemia Cells Killed in Culture by Immune Cells Grown from the Same Patient

Immune system natural killer (NK) cells were isolated from leukemia patients, expanded in culture, and then shown in an in vitro system to attack and destroy cancer cells from the original cell donors.

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.

Investigators at the University of Southern California (Los Angeles, USA; www.usc.edu) used flow cytometry to determine that ALL patient samples at diagnosis, post-induction, and relapse contained detectable numbers of CD56+ cells. They were able to selectively expand these CD56+ immune effector (NK) cells from bone marrow and peripheral blood samples at diagnosis and at various stages of treatment by co-culture with artificial antigen-presenting K562 clone 9.mbIL-21 cells. They combined these expanded immune effector cells with a monoclonal antibody targeted to a specific receptor (BAFF-R) on the leukemia cells.

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.

Results revealed that matched CD56+ effector cells killed autologous ALL cells grown out from leukemia samples of the same patient, through both spontaneous as well as antibody-dependent cellular cytotoxicity. Since autologous cell therapy avoids the potential development of graft-versus-host disease, these results indicate that expanded CD56+ cells could be applied for treatment of pre-B-ALL without transplantation, or for purging of bone marrow in the setting of autologous bone marrow transplants.

"In this study, we used NK cells and ALL cells from the same pediatric patients. We found that autologous natural killer cells will destroy the patient's leukemia cells," said senior author Dr. Nora Heisterkamp, professor of research, pediatrics, and pathology at the University of Southern California.

Blocking Nerve Growth Factor Receptor Enables Human Nervous System Regeneration

cont'd from cover

that the p75 neurotrophin receptor, a member of the tumor necrosis factor receptor superfamily, was required as a co-receptor for the Nogo receptor (NgR - reticulon 4 receptor) to mediate the activity of regeneration inhibitors such as Nogo. The Nogo receptor mediates axonal growth inhibition and may play a role in regulating axonal regeneration and plasticity in the adult central nervous system.

p75, also called nerve growth factor receptor, contains an extracellular domain containing four 40-amino acid repeats with six cysteine residues at conserved positions followed by a serine/threonine-rich region, a single transmembrane domain, and a 155-amino acid cytoplasmic domain. The cysteine-rich region contains the nerve growth factor binding domain.

In the current study, the investigators used a protein, p45, known to stimulate nervous system regeneration in lower animals but lacking in humans. They found that when added to cultures of human neurons, p45 markedly interfered with the function of p75 as a co-receptor for NgR. p45 bound p75 through both its transmembrane (TM) domain and death domain (DD).

To understand the underlying mechanisms, they determined the three-dimensional NMR solution structure of the intracellular domain of p45 and characterized its interaction with p75. They identified the residues involved in this interaction by NMR and co-immunoprecipitation.

Results of these structural and functional studies published in the August 5, 2014, online edition of the journal *PLOS Biology* revealed that p45 bound specifically to conserved regions in the p75 transmembrane domain and in the intracellular domain and that this binding blocked p75 dimerization along with its downstream signaling. Blocking the activity of p75 allowed nervous tissue to regenerate.

"This research implies that we might be able to mimic neuronal repair processes that occur naturally in lower animals, which would be very exciting," said senior author Dr. Kuo-Fen Lee, professor of molecular neurobiology at the Salk Institute for Biological Studies. "We do not know why this nerve regeneration does not occur in humans. We can speculate that the brain has so many neural connections that this regeneration is not absolutely necessary."

Inverted Microscope Designed to Readily Adapt to Changing Research Demands

cont'd from cover

Modularity is the key concept defining the new Leica Microsystems DMi8 inverted microscope, and the core of this concept is the unique illumination port, the "Infinity Port." This port facilitates the integration of additional light sources and laser systems for advanced applications.

To augment the Infinity Port, the Leica DMi8 boasts an innovative closed-loop focus system accurate to 20 nm over a 12 mm travel range, which enables researchers to scan large specimens with high precision.

Modules available for use with the DMi8 allow the user to take advantage of the full range of contrast methods from brightfield, integrated modulation contrast, phase contrast to darkfield, differential interference contrast, and fluorescence.

Use of different analysis channels for different fluorescence stains allows the user to analyze several aspects of a sample at the same time. An individual workflow can be assigned to each analysis channel. For example a binary reference mask can be applied to obtain object specific data, such as counting the number of spots in each nucleus. Alternatively, multiple analysis channels can be applied to the same image. Healthy cells can be counted on a stained color image in one analysis channel while a second analysis channel is used to count abnormal cells.

"The Leica DMi8 is an open and freely configurable inverted research microscope which meets the current and future needs of life scientists in a single platform," said Bernard Kleine, product manager at Leica Microsystems (Wetzlar, Germany; www.leica-microsystems.com). "Universality and individuality have been the heart of our development work. With the Leica DMi8 we serve customer needs ranging from plain microscopy to advanced research applications, and pay heed to the fact that tasks and applications in research change. The Leica DMi8 combines the versatility of an open platform with the user-friendliness of a system solution."

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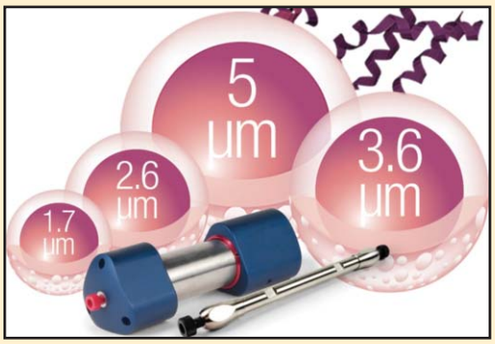

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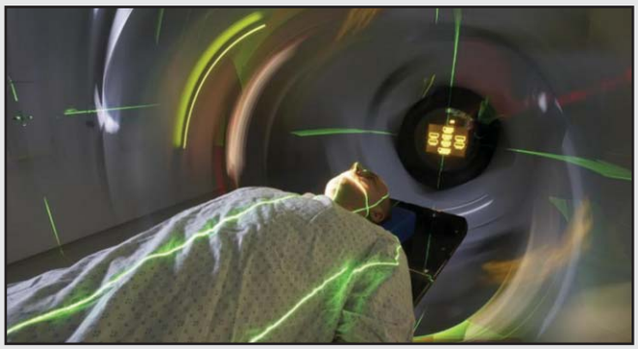
Naturally Derived Plant Compounds Protect Skin During Cancer Radiotherapy



Plant-derived natural compounds may provide protection to the skin from the damaging effects of gamma radiation during cancer radiotherapy, according to new research.

Radiotherapy for cancer involves exposing the patient or their tumor more directly to ionizing radiation, such as X-rays or gamma rays. The radiation irreparably injures the cancer cells. Regrettably, such radiation is also harmful to healthy tissue, in particular, the skin over the site of the tumor, which is then at risk of hair loss, skin problems, and even skin cancer. Because of these disadvantages, finding ways to protect the overlying skin are being actively sought.

Writing in the August/September 2014 issue of the *International Journal of Low Radiation*, Dr. Faruck Lukmanul Hakkim, from the University of Nizwa (Oman; www.unizwa.edu.om) and Nagasaki University (Japan; www.nagasaki-u.ac.jp), and colleagues from Macquarie University (Sydney, NSW, Australia; http://mq.edu.au), Bharathiar University (Coimbatore, Tamil Nadu, India; www.b-u.ac.in) and Konkuk University (Seoul, Republic of Korea; www.konkuk.ac.kr), explained how three abundant and well-evaluated natural products derived from plants can protect the skin against gamma radiation during radiotherapy.

Dr. Hakkim and colleagues discussed in their article the benefits of the organic, antioxidant compounds caffeic acid (CA), rosmarinic acid (RA), and transcinnamic acid (TCA) used at nontoxic concentrations. They assessed the radio-protective effect of these compounds against gamma-radiation in terms of reducing levels of reactive oxygen species (ROS) generated in skin cells by clinical relevance dose of gamma ray in the laboratory and in terms of the damage to the genetic material DNA, specifically double strand breaks in laboratory samples of human skin cells (keratinocytes).

The investigators discovered that treating the human skin cells with CA, RA, and TCA can protect the cells by 40, 20, and 15%, respectively, from gamma ray toxicity. The scientists suggested that the protective effect occurs because the compounds soak up the ROS and chemically deactivate them as well as enhancing the body's natural DNA repair processes.

The investigators suggested that these compounds would be well suited to be used as skin protectants during combination chemo- and radiotherapy. Further research is ongoing to study the clinical potential of mixtures of the three natural products.

Image: A study shows that certain compounds derived from plants might help cancer patients better cope with the effects of radiotherapy (Photo courtesy of the International Journal of Low Radiation).

Researchers Show How the Influenza Virus Blocks Natural Killer Cell Recognition

A team of molecular virologists has described how the influenza virus evolved a defense mechanism to protect it from attack by the immune system's natural killer (NK) cells.

The recognition of pathogen-infected cells by the immune system's NK cells is controlled by inhibitory and activating receptors. Investigators at the Hebrew University of Jerusalem (Israel; www.huji.ac.il) had shown previously that among the activating NK cell receptors, the natural cytotoxicity receptors NKp44 and NKp46 interacted with the viral hemagglutinin (HA) protein expressed on the cell surface of influenza-virus-infected cells. The interaction between NKp44/NKp46 and viral HA was sialic-acid dependent, and the recognition of HA by NKp44 and NKp46 led to the elimination of the infected cells.

In the current study, which was published in the August 1, 2014, issue of the *Journal of Infectious Diseases*, the investigators demonstrated that the influenza virus developed a counter-attack mechanism based on the virus' neuraminidase (NA) protein. The NA enzyme removed HA sialic acid and prevented the recognition of the virus by the NKp44 and NKp46 receptors. This lack of recognition resulted in reduced elimination of the infected cells by NK cells.

Understanding the NA/HA interaction and its influence on NK cell behavior is expected to lead to the development of new approaches for treating influenza.

Influenza is a major global health problem causing approximately three to five million cases of severe illness and leading to between 250,000 and 500,000 deaths worldwide. "It is thus urgent to develop new drugs for fighting influenza infection, which requires an understanding of the virus's life cycle and its interaction with the host's immune system," said first author Yotam Bar-On, a research student in immunology and oncology at the Hebrew University of Jerusalem.

In recognition of the significance of his research, Yotam Bar-On was recently awarded the prestigious Kaye Innovation Award. This award was established by the prominent British pharmaceutical industrialist Isaac Kaye to encourage faculty, staff, and students of the Hebrew University of Jerusalem to develop innovative methods and inventions with good commercial potential that will benefit the university and society.

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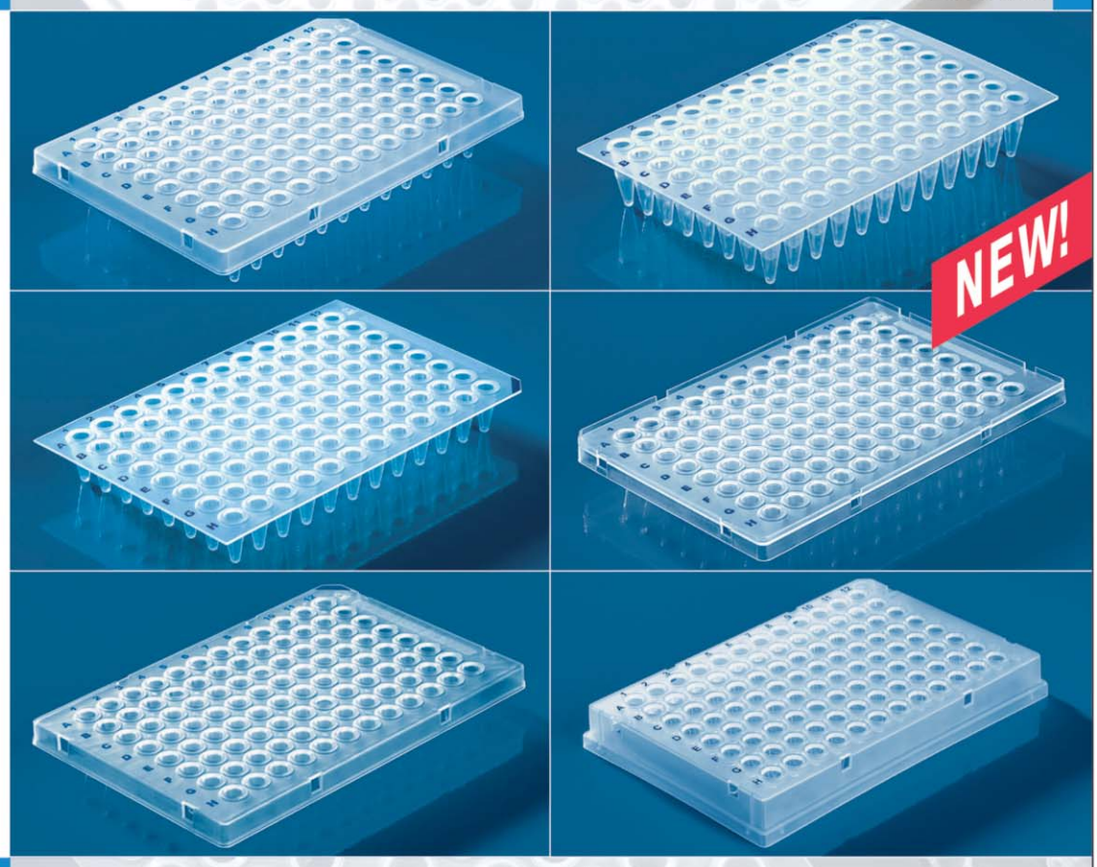

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Elevated Levels of IgG2 Antibodies Protect Some Types Of Gram-Negative Bacteria

The finding that an overabundance of a certain class of antibodies protects some bacteria from the effects of antibiotics has marked implications for our understanding of the protection generated by natural infections and for the design of vaccines, which should avoid inducing such inhibitory antibodies.

Investigators at the University of Birmingham (United Kingdom; www.birmingham.ac.uk) worked with patients that had bronchiectasis – a chronic infection characterized by persistent cough, shortness of breath, and chest pain – or lung infection caused by the bacterium *Pseudomonas aeruginosa*.

They reported in the August 2014 online edition of the *Journal of Experimental Medicine* that in a significant portion of these patients, antibodies protected the bacterium from complement-mediated killing. Strains that resisted antibody-induced, complement-mediated killing produced a lipopolysaccharide containing O-antigen. In particular, they found that inhibition of antibody-mediated killing was caused by excess production of O-antigen–specific antibodies of the IgG2 class. Depletion of IgG2 to O-antigen restored the ability of sera to kill strains with long-chain O-antigen.

Patients with impaired serum-mediated killing of *P. aeruginosa* by IgG2 were shown to have poorer respiratory function than infected patients who did not produce the inhibitory antibody.

The authors suggested that excessive binding of IgG2 to O-antigen shielded the bacterium from other antibodies that could induce complement-mediated killing. Since there is significant sharing of O-antigen structure between different Gram-negative bacteria, this IgG2-mediated impairment of killing could be operating in other Gram-negative infections as well. These findings have marked implications for understanding the nature of protection generated by natural infections and for the design of vaccines, which should avoid inducing IgG2 class inhibitory antibodies.

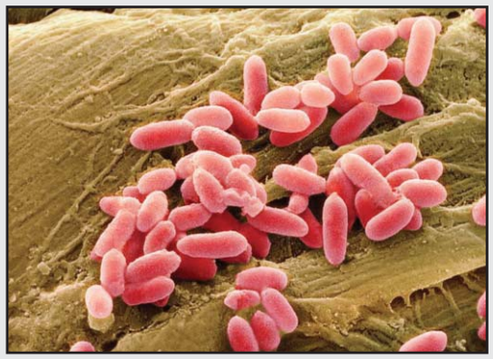


Image: Colored scanning electron micrograph (SEM) of Pseudomonas aeruginosa bacteria, a cause of serious wound, lung, skin, and urinary tract infections (Photo courtesy of Steve Gschmeissner / FineArtAmerica).

Two-Dimensional Infrared Spectroscopy Offers Clues into Amyloid Disease Mechanisms

Amyloid diseases, such as type 2 diabetes, cataracts, Alzheimer's disease, and the spongiform encephalopathies, all share the common characteristic that proteins aggregate into long fibers that then form plaques. However, recent in vitro research has demonstrated that neither the amylin monomer precursors nor the plaques themselves are very toxic. New data revealed by using two-dimensional infrared (2D IR) spectroscopy shows an intermediate structure during the amylin aggregation pathway that may clarify toxicity, offering new strategies for interventions.

The findings were published in the online July 1, 2014, in the journal *Biomedical Spectroscopy and Imaging*. "Figuring out how and why amyloid plaques form is exceedingly difficult, because one needs to follow the atomic shapes of the protein molecules as they assemble. Most tools in biology give either shapes or motions, but not both. We have been developing a new spectroscopic tool, called two-dimensional infrared spectroscopy, which can monitor the plaques as they form in a test tube," said lead investigator Martin T. Zanni, PhD, from the department of chemistry at the University of Wisconsin-Madison (USA; www.wisc.edu).

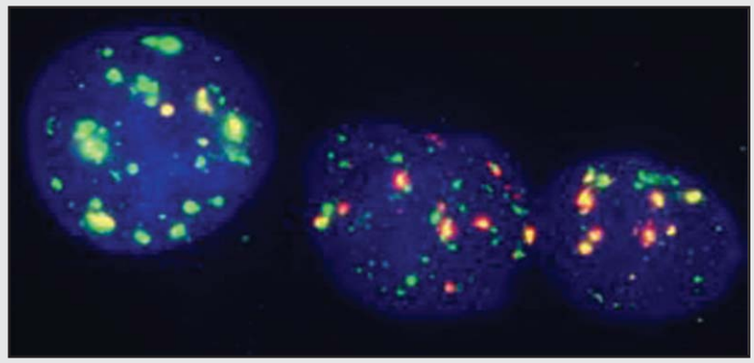
The researchers utilized this new technology to study the amyloid protein associated with type 2 diabetes. Isotope labeling was used to measure the secondary structure content of individual residues. By following many 2D IR spectra from one particular region (known as the FGAIL region) over several hours, they were able to visualize the amylin as it progressed from monomers to fibers.

"We learned that, prior to making the plaques, the proteins first assemble into an unexpected and intriguing intermediate and organized structure," commented Dr. Zanni. The proteins undergo a transition from disordered coil (in the monomer), to ordered β-sheet (in the oligomer) to disordered structure again (in the fiber).

These findings help to elucidate the physics of the aggregation process, the chemistry of amyloid inhibitors, and the biology of type 2 diabetes, as well as elucidate earlier contradictory data.

The scientists suggest that differences between species in their capacity to develop type 2 diabetes may be related to the capacity to form these intermediate amylin structures. That may be why humans develop the disease while dogs and rats do not. "I am not encouraging us to begin engineering our DNA to match that of rats, but our findings may help to develop plaque inhibitors or hormone replacement therapies for people suffering from type 2 diabetes, because we know the structure we want to avoid," said Dr. Zanni. He added that mutations in the FGAIL region may inhibit fiber formation by interfering with the formation of these intermediates.

DNA Replication Difficulty May Be Key to Immune System Aging



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inability of blood-forming cells to maintain blood production over time in an old organism, and have identified molecular defects that could be restored for rejuvenation therapies," said Emmanuelle Passegué, PhD, a professor of medicine and a member of the Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research at the University of California, San Francisco (UCSF; USA; www.ucsf.edu). Dr. Passegué, a stem cell specialist, led a team that published their findings online July 30, 2014, in the journal *Nature*.

Blood and immune cells no not live long, and not like most tissues, must be continually replenished. The cells that must keep generating them throughout a lifetime are called hematopoietic stem cells. Through cycles of cell division these stem cells preserve their own numbers and generate the daughter cells that replenish replacement blood and immune cells. But the hematopoietic stem cells falter with age, because they lose the ability to replicate their DNA accurately and efficiently during cell division, Dr. Passegué's lab team determined.

Particularly susceptible to the degradation, the researchers discovered in their new study of older mice, are transplanted, aging, blood-forming stem cells, which no not have the ability to produce B cells of the immune system. These B cells generate antibodies to help treat many types of microbial infections, including bacteria that cause pneumonia, a leading killer of the older people.

In old blood-forming stem cells, the researchers found a lack of specific protein components needed to form a molecular machine called the mini-chromosome maintenance helicase, which unwinds double-stranded DNA so that the cell's genetic material can be duplicated and assigned to daughter cells later in cell division. In their study, the stem cells were stressed by the loss of activity of this machine, and as a result, were at heightened risk for DNA damage and death when forced to divide.

The researchers discovered that even after the stress associated with DNA replication, surviving, non-dividing, resting, old stem cells retained molecular tags on DNA-wrapping histone proteins, a feature often associated with DNA damage. However, the researchers determined that these old survivors could repair induced DNA damage as efficiently as young stem cells. "Old stem cells are not just sitting there with damaged DNA ready to develop cancer, as it has long been postulated," Dr. Passegué said.

The older surviving stem cells still had problems. The molecular tags accumulated on genes required to generate the cellular factories known as ribosomes. Dr. Passegué will further examine the concerns of reduced protein production as part of her ongoing research. "Everybody talks about healthier aging," he added. "The decline of stem-cell function is a big part of age-related problems. Achieving longer lives relies in part on achieving a better understanding of why stem cells are not able to maintain optimal functioning."

Dr. Passegué hopes that it might be possible to prevent declining stem-cell populations by developing a medicine to prevent the loss of the helicase components required to effectively unwind and replicate DNA, thereby avoiding immune-system failure.

Image: Molecular tags of DNA damage are highlighted in green in blood-forming stem cells (Photo courtesy of UCSF).

Surface Protein Protects Brain Tumor Cells from Immune Attack

Malignant glioma brain tumor cells suppress the natural killer cell (NK) immune response by over expressing the surface protein galectin-1, and suppression of this protein renders the tumor cells susceptible to destruction by the immune system.

Galectin-1 (LGALS1 lectin, galactoside-binding, soluble, 1) is a member of the galectin family of beta-galactoside-binding proteins, which has been implicated in modulating cell-cell and cell-matrix interactions. This protein may act as an autocrine negative growth factor that regulates cell proliferation. Autocrine signaling is a form of cell signaling in which a cell secretes a hormone or chemical messenger (called the autocrine agent) that binds to autocrine receptors on that same cell, leading to changes in the cell.

Investigators at the University of Michigan (Ann Arbor, USA; www.umich.edu) had been studying gliomas, which make up about 80% of all malignant brain tumors, including anaplastic oligodendrogliomas, anaplastic astrocytomas, and glioblastoma multiforme.

In the current study, they used rodent models to demonstrate that malignant glioma cells suppressed NK immune surveillance by over expressing galectin-1. Conversely, galectin-1 deficient glioma cells could be eradicated by host NK cells prior to the initiation of an anti-tumor T-cell response. Results of in vitro experiments published in the July 18, 2014, online edition of the journal *Cancer Research* demonstrated that galectin-1 deficient GL26-Cit glioma cells were nearly three times more sensitive to NK-mediated tumor lysis than galectin-1 expressing cells.

"This is an incredibly novel and exciting development, and shows that in science we must always be open-minded and go where the science takes us; no matter where we thought we wanted to go," said senior author Dr. Pedro Lowenstein, professor of neurosurgery at the University of Michigan. "In this case, we found that over-expression of galectin-1 inhibits the innate immune system, and this allows the tumor to grow enough to evade any possible effective T-cell response. By the time it is detected, the battle is already lost."

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Stem Cell Advance May Enhance The Process of Tissue Regeneration

A new stem-cell discovery might one day lead to a more streamlined way to obtain stem cells, which then could be used in the development of replacement tissue for declining body parts.

The research builds on a strategy exploited by scientists from the University of California, San Francisco (UCSF; USA; www.ucsf.edu) that involves reprogramming adult cells back to an embryonic state in which they again have the potential to become any type of cell. They reported their findings July 17, 2014, issue of the journal *Cell*.

The efficiency of this process may soon increase due to the scientists' identification of biochemical pathways that can suppress the necessary reprogramming of gene activity in adult human cells. Taking away these hurdles was shown to increase the efficiency of stem-cell production.

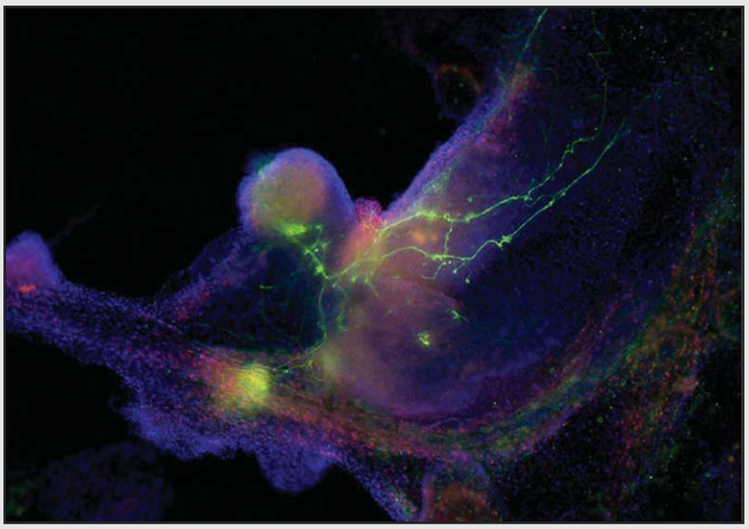
"Our new work has important implications for both regenerative medicine and cancer research," said Miguel Ramalho-Santos, PhD, an associate professor of obstetrics, gynecology and reproductive sciences and a member of the Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research at UCSF, who led the research, funded in part by a NIH Director's New Innovator Award.

The earlier discovery that it was possible to take specialized adult cells and reverse the developmental clock to strip the mature cells of their distinguishing identities and characteristics, and to make them immortal, reprogrammable cells that theoretically can be used to substitute for any tissue type, led to a share of the Nobel Prize in Physiology or Medicine being awarded to UCSF, Gladstone Institutes and Kyoto University (Japan) researcher Shinya Yamanaka, MD, in 2012.

These induced pluripotent stem (iPS) cells are regarded as an alternative research strategy to ongoing efforts to develop tissue from stem cells obtained from early-stage human embryos. However, in spite of the potential of iPS cells and the enthusiasm surrounding iPS research, the percentage of adult cells effectively transformed to iPS cells is typically low, and the resulting cells often retain indications of their earlier lives as specialized cells.

Researchers generate stem cells by forcing the activation within adult cells of pluripotency-inducing genes, beginning with the so-called "Yamanaka factors," a process that turns back the clock on cellular maturation. However, as Dr. Ramalho-Santos noted, "from the time of the discovery of iPS cells, it was appreciated that the specialized cells from which they are derived are not a blank slate. They express their own genes that may resist or counter reprogramming."

But as to what precisely was getting in the way of reprogramming remained little understood. "Now, by genetically removing multiple barriers to reprogramming, we have found that the efficiency of generation of iPS cells can be greatly increased," Dr. Ramalho-Santos said. The discovery, he reported, will contribute to accelerating the safe and effective use of iPS cells and other reprogrammed cells.



The researchers found not only isolated genes acting as barriers, but rather sets of genes acting together through different mechanisms to create roadblocks to reprogramming. "At practically every level of a cell's functions there are genes that act in an intricately coordinated fashion to antagonize reprogramming," Dr. Ramalho-Santos said.

These processes are likely to help adult cells maintain their characteristics and functional roles. "Much like the Red Queen running constantly to remain in the same place in Lewis Carroll's 'Through the Looking-Glass,' adult cells appear to put a lot of effort into remaining in the same state," he said.

To uncover this earlier unidentified busy biochemical environment of inhibitory gene activity, the scientists had to simultaneously master a few different technical coups in the lab. They combined advanced cellular, genetic, and bioinformatics technologies to comprehensively identify genes that act as barriers to the generation of human iPS cells, and examined how these distinctive barriers work.

Apart from maintaining the stability of adult tissues, the barrier genes most likely serve important roles in other diseases – including in the prevention of various cancers, according to Dr. Ramalho-Santos.

Image: Molecular tags of DNA damage are highlighted in green in blood-forming stem cells (Photo courtesy of UCSF).

Brain Tumors Grow by Tapping Preexisting Blood Vessels for Nutrients

Findings from a new study on how tumors grow and spread in the brain may cause cancer researchers to rethink treatment options based on drugs that block angiogenesis.

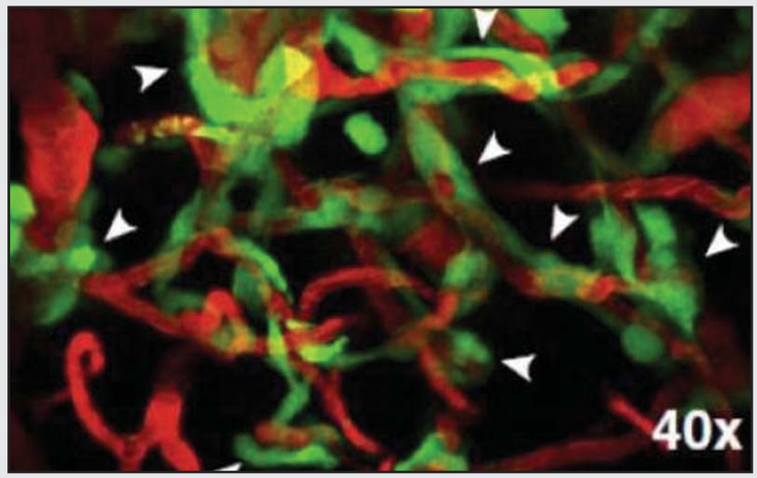
According to the angiogenesis theory, tumors that are more than one cubic millimeter in size need to attract or grow their own blood vessels to survive. This theory led to clinical trials with anti-angiogenesis drugs such as bevacizumab and DC101. However, such clinical trials have failed to produce evidence of reduced tumor growth or increased patient survival.

Investigators at the University of Michigan (Ann Arbor, USA; www.umich.edu) examined this phenomenon in rodents and human cancer patients and by advanced computer modeling.

They reported in the July 2014 issue of the journal *Neoplasia* that implanted rodent and human brain cancer cells commonly invaded and proliferated within the brain perivascular space. This form of brain tumor growth and invasion was also shown to characterize de novo generated endogenous mouse brain tumors, biopsies of primary human glioblastoma, and peripheral cancer metastasis to the human brain.

Perivascularly invading brain tumors became vascularized by normal brain microvessels when individual glioma cells used perivascular space as a conduit for tumor invasion. Since the cancer cells were obtaining blood from already existing vascular tissues, their growth and spread were not impeded by treatment with antiangiogenic agents.

The experimental findings showing that tumor perivascular spreading was independent of growth of new blood vessels had been predicted by computational modeling. The investigators tested this prediction experimentally by blocking angiogenic signaling using antibodies targeting the VEGF-A (vascular endothelial growth factor) signaling axis. VEGF-A inhibitors failed to block progressive tumor growth or extend median survival in multiple brain tumor models.



"The key question has been to determine how tumor-generating cells grow to form the macroscopic tumor mass that eventually kills the patients," said senior author Dr. Pedro Lowenstein, professor of neurosurgery and cell and developmental biology at the University of Michigan. "We have shown that because of the very high density of endogenous vessels in the brain and central nervous system, the cells grow along those preexisting vessels and eventually divide to fill the space between them, where the distance between any two vessels is very small. This iterative growth along vessels and into the space between means the tumor does not grow like a balloon requiring new vessels to grow into its expanding mass to rescue it, but rather as an accumulation of local small masses which then coalesce into a large tumor."

Image: Microscopic view of a mouse brain tumor showing small clusters of tumor cells (in green), marked with white arrows, growing along tiny blood vessels (in red) in the brain and filling the space in between the vessels (Photo courtesy of the University of Michigan Medical School).

Shape Memory Polymer Designed to Help Reconstruct Faces

Researchers have developed a "self-fitting" material that expands with warm salt water to effectively fill bone defects, and also acts as a scaffold for new bone growth.

Birth defects, such as cleft palates, injuries, or surgery to remove a tumor can create gaps in bone that are too large to heal naturally. Furthermore, when they occur in the head, face, or jaw, these bone defects can dramatically alter an individual's appearance.

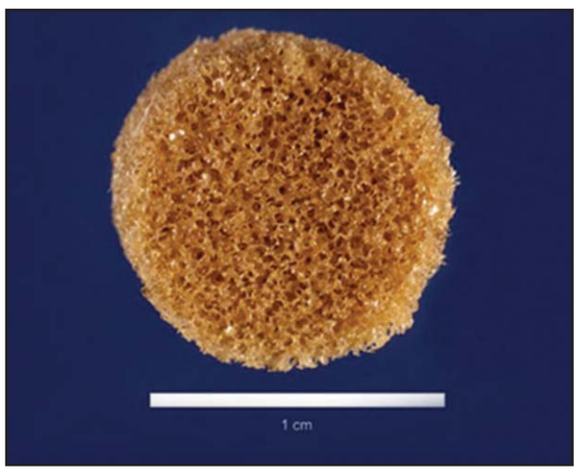
The researchers described their approach at the 248th National Meeting & Exposition of the American Chemical Society (ACS), the world's largest scientific society, on August 13, 2014, held in San Francisco (CA, USA). Currently, the most common way to fill bone defects in the face, head, or jaw (the cranio-maxillofacial area) is autografting: a process in which surgeons harvest bone from somewhere else in the body, such as the hip bone, and then try to shape it to fit the bone defect. "The problem is that the autograft is a rigid material that is very difficult to shape into these irregular defects," said Melissa Grunlan, PhD, leader of the study.

Moreover, harvesting bone for the autograft can itself create complications at the place where the bone was taken. Another strategy is to use bone putty or cement to fill gaps. However, these materials are not ideal. They become very brittle when they harden, and they do not have pores, or small holes, that permit new bone cells to move in and reconstruct the damaged tissue.

To develop a better material, Dr. Grunlan and her colleagues from Texas A&M University (College Station, USA; www.tamu.edu) constructed a shape-memory polymer (SMP) that molds itself precisely to the shape of the bone defect without being brittle. It also supports the growth of new bone tissue.

SMPs are materials whose geometry changes in response to heat. The investigators made a porous SMP foam by linking together molecules of poly(ε-caprolactone), an elastic, biodegradable substance that is already used in some medical implants. The resulting material resembled a stiff sponge, with many interconnected pores to allow bone cells to migrate in and grow. Upon heating to 60 °C, the SMP becomes very soft and pliable. Therefore, during surgery to repair a bone defect, a surgeon could warm the SMP to that temperature and fill in the defect with the softened substance. Then, as the SMP is cooled to body temperature, it would resume its former stiff texture and "lock" into place.

The researchers also coated the SMPs with polydopamine, a sticky substance that helps lock the polymer into position by inducing formation of a mineral that is found in bone. It may also help osteoblasts, the cells that generate bone, to stick and spread throughout the polymer. The SMP is biodegradable, so that eventually the scaffold will disappear, leaving only new bone tissue behind.



To evaluate whether the SMP scaffold could support bone cell growth, the researchers seeded the polymer with human osteoblasts. After three days, the polydopamine-coated SMPs had grown about five times more osteoblasts than those without a coating. Furthermore, the osteoblasts produced more of the two proteins, runX2 and osteopontin, which are critical for new bone formation.

Dr. Grunlan reported that the next phase of the research will be to evaluate the SMP's ability to heal cranio-maxillofacial bone defects in animals. "The work we've done in vitro is very encouraging," she says. "Now we'd like to move this into preclinical, and hopefully, clinical studies."

Image: Shape-Memory Polymer (SMP). A new material that expands with warm salt water fills bone defects is also a scaffold for new bone growth (Photo courtesy of Dr. Melissa Grunlan / Texas A&M University).

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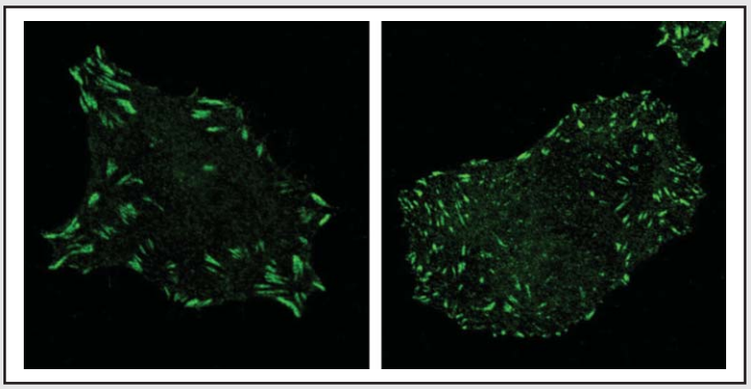
Molecular Pathway Decreases Cell Adhesion and Initiates Metastasis



A recent paper outlined a molecular pathway that enables lung cancer cells to migrate away from the site of the primary tumor and become established in other parts of the body. Investigators at the Salk Institute for Biological Studies (La Jolla, CA, USA; www.salk.edu) linked a virtual alphabet soup of genes and their protein products to the epithelial-to-mesenchymal transition (EMT) that is a prerequisite for metastasis.

The serine/threonine kinase LKB1 (liver kinase B1) is a tumor suppressor gene whose loss is associated with increased metastatic potential. In an effort to define biochemical signatures of metastasis associated with LKB1 loss, the investigators discovered that the EMT transcription factor Snail1 was uniquely upregulated upon LKB1 deficiency across cell types. Snail1 is a central regulator of epithelial cell adhesion and movement in EMTs during embryo development; a process reactivated during cancer metastasis. The ability of LKB1 to suppress Snail1 levels was independent of AMPK (AMP-activated protein kinase) but required the related kinases MARK1 (MAP/microtubule affinity-regulating kinase 1) and MARK4 (MAP/microtubule affinity-regulating kinase 4).

In a screen for substrates of the kinases involved in Snail regulation, the investigators identified the scaffolding protein DIXDC1 (DIX domain containing 1), a positive regulator of the Wnt signaling pathway that is associated with gamma tubulin at the centrosome. Similar to loss of LKB1, DIXDC1 depletion resulted in upregulation of Snail1 in a FAK (Focal Adhesion Kinase)-dependent manner, leading to increased cell invasion. FAK is a focal adhesion-associated protein kinase involved in cellular adhesion and spreading processes. It has been shown that when FAK was blocked, breast cancer cells became less metastatic due to decreased mobility.

MARK1 phosphorylation of DIXDC1 was required for its localization to focal adhesions and ability to suppress metastasis in mice. DIXDC1 is frequently downregulated in human cancers, which correlates with poor survival.

"Lung cancer, even when it is discovered early, is often able to metastasize almost immediately and take hold throughout the body," said senior author Dr. Reuben J. Shaw, professor of molecular and cell biology at the Salk Institute for Biological Studies. "The reason behind why some tumors do that and others do not has not been very well understood. Now, through this work, we are beginning to understand why some subsets of lung cancer are so invasive. The good news is that this finding predicts that patients missing either gene should be sensitive to new therapies targeting focal adhesion enzymes, which are currently being tested in early-stage clinical trials."

The study was published in the July 17, 2014, online edition of the journal *Molecular Cell*.

Image: Focal adhesion complexes (bright green) are typically large and sticky, anchoring a cell into place (left). When the gene DIXDC1 is knocked out, focal adhesion complexes instead become small and numerous, readying cancer cells to move into the bloodstream and become metastatic (right) (Photo courtesy of the Salk Institute for Biological Studies).

Bead-Based Assay Kits to Boost Metabolic and Hormone Research

A line of magnetic bead, microtiter plate-based metabolic assay kits is now available for use by biotech and other life science researchers.

The Bio-Rad Laboratories, Inc. (Hercules, CA, USA; www.bio-rad.com) Bio-Plex Pro RBM Human Metabolic and Hormone Assay line comprises kits for the analysis of seven panels of highly relevant biomarkers involved in diabetes, obesity, metabolic syndrome, cardiovascular disease (CVD), and hormonal control of metabolism and reproductive organs. The kits were developed in partnership with Myriad RBM, Inc., (Austin, TX, USA; http://rbm.myriad.com).

In the standard format, each kit contains one 96-well microtiter plate, magnetic capture beads, detection antibodies, standards, two-level controls, diluent, buffers, streptavidin-PE, and plate seals for the detection of up to eight human metabolic markers.

The assays are built on a magnetic bead platform, which allows data to be reported within three and a half hours. The kit format enables robust quantification of multiple proteins in human serum, plasma, and cell culture media samples. Kits are offered for research involving gut hormones and adipokines, pituitary hormones, diabetes (type I and type II), metabolic syndrome, obesity, CVD, and inflammation.

The Bio-Plex Pro RBM Human Metabolic and Hormone Assay line of kits is compatible with the Bio-Plex 100/200, Bio-Plex 3-D, and Bio-Plex MAGPIX analytical platforms, as well as all other Luminex-based xMAP instruments and software.

Desorption Electrospray Ionization Mass Spectrometry Imaging Guides Removal of Brain Tumors

US researchers have developed an imaging system that rapidly and accurately detects a molecular marker found in brain gliomas. The technology has the potential to optimize the precision of these difficult surgeries by enabling the total removal of the tumor, while reducing residual damage to brain tissue and neural function.

During tumor surgery, surgeons try to remove tumor tissue without damaging surrounding healthy tissue. This is particularly critical when removing brain gliomas, as damage to adjacent healthy brain tissue can have significant effects on the patient's neural function. Conversely, if cancerous tissue is not completely removed, the tumor may grow back. To address these issues, US National Institute of Biomedical Imaging and Bioengineering (NIBIB; Bethesda, MD, USA; www.nibib.nih.gov)-funded researchers have developed an imaging system that rapidly and accurately detects a molecular marker found in brain gliomas.

The imaging system is known as desorption electrospray ionization mass spectrometry (DESI MS). The technique was developed by R. Graham Cooks, PhD, from Purdue University (West Lafayette, IN, USA; www.purdue.edu), the brain study was conducted with collaborators at Harvard Medical School (Boston, MA, USA; http://hms.harvard.edu) and Dana Farber Cancer Institute (Boston, MA, USA; www.dana-farber.org), and the findings were published in the June 30, 2014, issue of the *Proceedings of the National Academy of Sciences of the United States of America (PNAS)*. DESI MS has the potential to be a considerable improvement over the current method of differentiating brain tumor tissue from healthy tissue, which relies on an extremely lengthy and difficult procedure for surgeons and patients.

The current protocol uses frozen section pathology, which involves removing suspected tumor tissue and having it analyzed by pathologists. They use a freezing and staining method that takes about 20 minutes and is too slow to be repeated multiple times during surgery. This method, developed more than 150 years ago, is both inefficient and lacks precision. It can result in incomplete tumor removal and regrowth, as well as inadvertent damage to healthy tissue, which can cause significant deficits in functioning for patients.

The new technique solves some of the problems of the current method. Researchers use the ability of mass spectrometry to identify metabolites that are present in brain tumors, but not in healthy tissue. As surgery progresses, tissue samples are removed and sprayed with a charged liquid that splashes onto the surface of the tissue, lifting off droplets; the droplets are then sucked into a mass spectrometer, where the mass and charge of the metabolites are measured. Brain gliomas produce large amounts of a tumor metabolite, 2-hydroxyglutarate (2-HG), which is captured in the liquid. This very rapid, objective modality allows for clear delineation of tumor versus non-tumor tissue, therefore, surgeons can remove all, and only, tumor tissue.

The DESI MS system was first tested on glioma specimens from 35 patients. Twenty-one of the 35 samples contained high levels of 2-HG, a product of the mutant form of a gene known as IDH, which is associated with tumor formation. The findings distinctly demonstrated that DESI MS can detect 2-HG in tumor tissue with very high sensitivity and specificity.

The researchers went on to evaluate the system in an operating room. The group installed a complete DESI MS system in the Advanced Multimodality Image Guided Operating (AMIGO) suite at Brigham and Women's Hospital (Boston, MA, USA), which is a part of the National Center for Image-Guided Therapy. The AMIGO surgical suite is an operating room with built-in imaging devices such as a magnetic resonance imaging (MRI) system, so the surgeon can use it to map the tumor preoperatively. Tissue sections from tumors from two patients were examined using DESI MS. In both instances, the postoperative analysis confirmed that intraoperative DESI MS had effectively detected the presence of 2-HG in each tumor.

The researchers chose detection of 2-HG to test the DESI MS system because approximately 80% of gliomas and glioblastomas are associated with mutations in the IDH gene, which results in high levels of 2-HG. This approach described could be used for the resection of all 2-HG-producing tumors.

Gliomas are tumors comprised of brain glial cells and account for most of malignant brain tumors in adults. Gliomas comprise approximately 30% of all brain and central nervous system (CNS) tumors and 80% of all malignant brain tumors. This research provides proof-of-concept of the accuracy and effectiveness of the DESI MS system, according to the investigators, and suggests that the system can be used with this common 2-HG-producing tumor, as well as other tumors in which a metabolic marker of malignancy is produced.

The DESI MS system was shown to be very accurate and was easily adapted for use in the clinical setting. It does not have the limitations of magnetic resonance imaging (MRI), which cannot provide information about the type of tumor, and requires that surgery be halted for an hour or longer for scanning and interpretation of findings. Moreover, each operating room that contains an MRI machine costs more than USD 10 million. By contrast, DESI MS platforms could be set up in any operating room at a very small fraction of the cost. The DESI MS system promises to be a powerful new tool for both research and clinical applications with the potential to transform surgical care of patients with brain tumors and other solid tumors.

Image: Livia Eberlin, PhD, operating a Desorption Electrospray Ionization Mass Spectrometry (DESI MS) system (Photo courtesy of Purdue University).

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Autistic Youngsters Found to Have Too Many Brain Synapses

Autistic children and adolescents have been shown to have an excess of brain synapses, and this is due to a slowdown in the normal brain "trimming" process during development, according to new findings.

Neuroscientists from Columbia University Medical Center (CUMC; New York, NY, USA; http://cumc.columbia.edu) conducted the research. Because synapses are the points where neurons connect and communicate with each other, the excessive synapses may have profound effects on how the brain functions. The study was published in the August 21, 2014, online issue of the journal *Neuron*.

The agent that restores normal synaptic pruning can improve autistic-like behaviors in mice, the researchers discovered; even when the drug is given after the behavior has appeared. "This is an important finding that could lead a professor and chair of psychiatry at CUMC and director of New York State Psychiatric Institute, who was not involved in the study.

Although the drug, rapamycin, has side effects that may preclude its use in people with autism, "the fact that we can see changes in behavior suggests that autism may still be treatable after a child is diagnosed, if we can find a better drug," said the study's senior investigator, David Sulzer, PhD, professor of neurobiology in the departments of psychiatry, neurology, and pharmacology at CUMC.

During normal brain development, a burst of synapse formation occurs in infancy, particularly in the cortex, a region involved in autistic behaviors; pruning eliminates about half of these cortical synapses by late adolescence. Synapses are known to be affected by many genes associated with autism, and some researchers have theorized that individuals with autism may have more synapses.

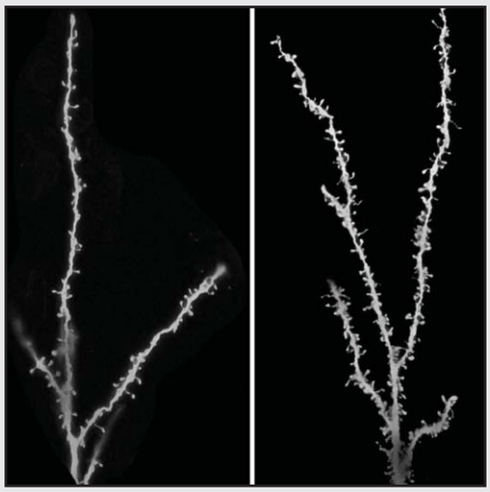
To evaluate this theory, coauthor Guomei Tang, PhD, assistant professor of neurology at CUMC, examined brains from children with autism who had died from other causes. Thirteen brains came from children ages 2 to 9, and 13 brains came from children ages 13 to 20. Twenty-two brains from children without autism were also examined for comparison.

Dr. Tang measured synapse density in a small section of tissue in each brain by counting the number of tiny spines that branch from these cortical neurons; each spine connects with another neuron via a synapse. By late childhood, spine density had decreased by approximately 50% in the control subjects' brains, but by only 16% in the brains from autism patients.

Insights into what caused the pruning defect were also found in the patients' brains; the autistic children's brain cells were filled with old and injured areas and were very deficient in a degradation pathway known as "autophagy."

The researchers could restore normal autophagy and synaptic pruning – and reverse autistic-like behaviors in the mice – by administering rapamycin, a drug that inhibits mTOR. The drug was effective even when administered to the mice after they developed the behaviors, suggesting that such an approach may be used to treat patients even after the disorder has been diagnosed.

Because large amounts of overactive mTOR were also found in almost all of the brains of the autism patients, the same processes may occur in children with autism. "What's remarkable about the findings," said Dr. Sulzer, "is that hundreds of genes have been linked to autism, but almost all of our human subjects had overactive mTOR and decreased autophagy, and all appear to have a lack of normal synaptic pruning. This says that many, perhaps the majority, of genes may converge onto this mTOR/autophagy pathway, the same way that many tributaries all lead into the Mississippi River. Overactive mTOR and reduced autophagy, by blocking normal synaptic pruning that may underlie learning appropriate behavior, may be a unifying feature of autism."



Alan Packer, PhD, senior scientist at the Simons Foundation, which funded the research, reported that the study is an important step forward in understanding what is occurring in the brains of people with autism. "The current view is that autism is heterogeneous, with potentially hundreds of genes that can contribute. That's a very wide spectrum, so the goal now is to understand how those hundreds of genes cluster together into a smaller number of pathways; that will give us better clues to potential treatments. The mTOR pathway certainly looks like one of these pathways. It is possible that screening for mTOR and autophagic activity will provide a means to diagnose some features of autism, and normalizing these pathways might help to treat synaptic dysfunction and treat the disease."

Image: Neurons in brains from people with autism do not undergo normal pruning during childhood and adolescence. The images show representative neurons from unaffected brains (left) and brains from autistic patients (right); the spines on the neurons indicate the location of synapses (Photo courtesy of Guomei Tang, PhD, and Mark S. Sonders, PhD / Columbia University Medical Center).

Drug for Treatment of Platinum Resistant Recurrent Ovarian Cancer Approved for Use in Europe

For the first time in more than 15 years the European Commission (EC) has approved a new therapeutic option for the most difficult to treat form of ovarian cancer.

Ovarian cancer causes more deaths than any other gynecologic cancer. It is the seventh most commonly diagnosed cancer in women worldwide, with an estimated 230,000 cases diagnosed around the world every year and there are approximately 150,000 deaths from the disease. In the European Union, there are an estimated 44,000 cases of ovarian cancer every year, and nearly 30,000 women will die from the disease.

The newly approved drug is bevacizumab, an antibody derived from Chinese hamster ovary cells combined with a mouse protein. It sold in the United States under the brand name Avastin and is manufactured by Genentech (San Francisco, CA, USA; www.gene.com), a subsidiary of Roche (Basel, Switzerland; www.roche.com).

Avastin works by blocking the action of vascular endothelial growth factor (VEGF). VEGF stimulates the growth of new blood vessels in the process known as angiogenesis. Avastin antibodies bind tightly to VEGF and inactivate it. As a result, new blood vessels are not formed, and cancer tumor growth is inhibited by lack of an adequate supply of blood. Treated tumors cannot get larger and may even shrink. Thus, Avastin does not work directly on the tumor, but prevents its growth by reducing its supply of blood.

The EC has now approved the use of Avastin in combination with the chemotherapeutic drugs paclitaxel, topotecan, or pegylated liposomal doxorubicin as a treatment for women with recurrent ovarian cancer that is resistant to platinum-containing chemotherapy. Approval was based on results of the phase III AURELIA study, which involved women with recurrent, platinum-resistant ovarian cancer who received either chemotherapy or Avastin in combination with chemotherapy. Results showed that the addition of Avastin to chemotherapy gave a clinically meaningful benefit, nearly doubling the median progression free survival (PFS) from 3.4 months to 6.7 months.

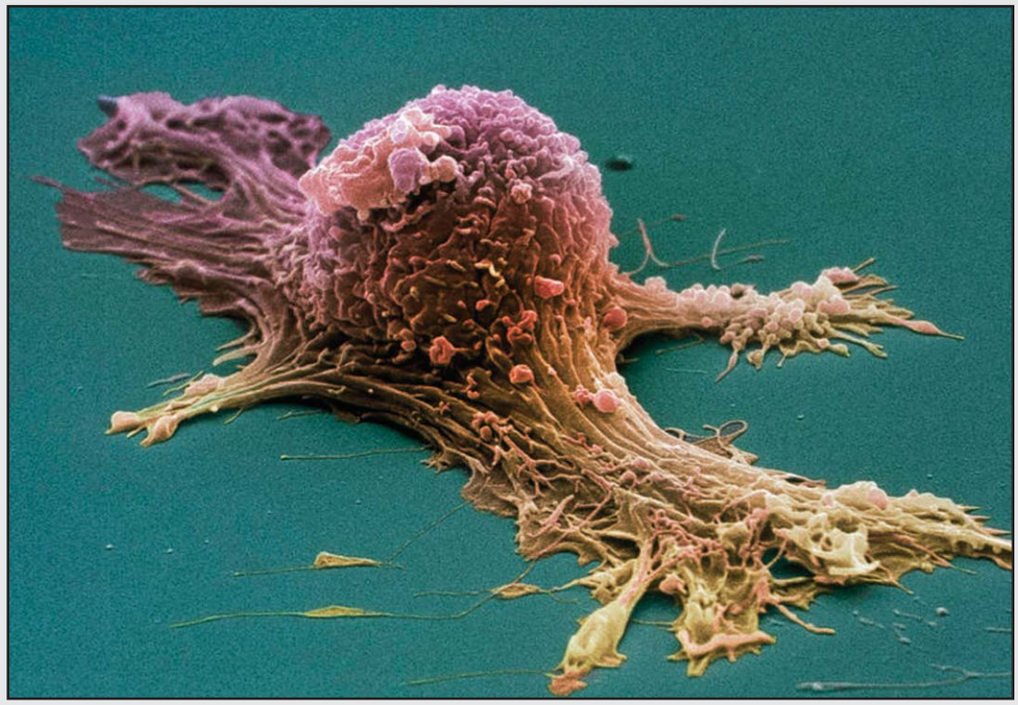


Image: Scanning electron micrograph (SEM) of an ovarian cancer cell (Photo courtesy of Steve Gschmeissner / SPL).

"European approval of Avastin for recurrent, platinum-resistant ovarian cancer is good news because Avastin can help women live longer without their cancer progressing, which is an important treatment goal in advanced disease," said Dr. Sandra Horning, chief medical officer and head of global product development at Roche. "Avastin is the first biologic medicine approved by the EU for women with this difficult to treat disease."

EU Data Protection Regulation May Put European Cancer Research at Risk

A European oncologic society's members are worried that a proposed European Union (EU) data protection regulation could make cancer research unfeasible and add a substantial burden to both physicians and cancer patients.

The European Society of Medical Oncology (ESMO; Lugano, Switzerland; www.esmo.org) has expressed concern that the proposed EU General Data Protection Regulation, published in the August 2014 issue of the journal *Annals of Oncology*, could make cancer research impossible. The planned wording of the regulation stipulates "explicit and specific patient consent," meaning that researchers would have to approach patients every time research is arranged to refer to their data or use tissue samples stored for research purposes.

"Hope for patients facing a life-threatening disease like cancer is based on advances in research," said Kathy Oliver, chair of the International Brain Tumor Alliance. "And research progress requires access to a wide pool of patient data, even from patients who have since passed away and can no longer provide consent to allow for research that could save lives in the future."

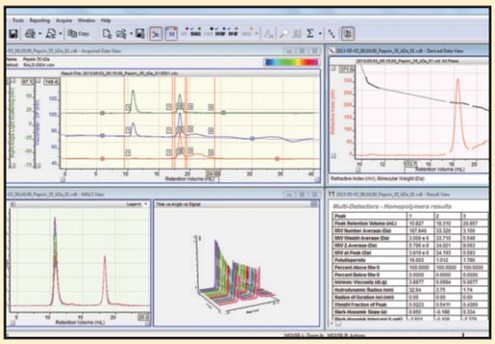
"This could put a halt to many public health research efforts," said ESMO president Rolf A. Stahel. ESMO proposes that the text of the EU General Data Protection Regulation includes a "one-time consent" for research, ensuring patients are aware of what they are consenting to – with the suitable safeguards in place, and that they can withdraw their consent at any time. "Our proposal achieves the correct balance between the right to privacy and the right to health. It actually empowers patients, allowing them to choose whether to donate their data and tissue for public health research, which has the ultimate goal of finding cures."

"As a cancer patient, I cannot think of any reason not to allow access to my data to help other patients receive better care and contribute to advancing cancer research," noted Hans Keulen, a Dutch rare cancer patient from the Chordoma Foundation (Durham, NC, USA).

Dr. Paolo G. Casali, ESMO Public Policy committee chair, author of the official ESMO position paper on the risks of the new EU Data Protection Regulation, said, "We understand the need for the EU to address data privacy concerns in many sectors, with the surge of risks brought about by the use of digital information, but its effect on public health research may have been unintentionally overlooked."

Population-based cancer registries, for example, storing information to track disease trends, are inherently incompatible with any requirement of individual consent, "If a patient is allowed not to consent use of his/her anonymized data for the registry, the data provided by that registry will be unrepresentative and can lead to incorrect conclusions for public health actions," noted Dr. Casali.

ESMO is in favor of inclusion in the EU General Data Protection Regulation of the withdrawable "one-time consent" strategy – already forecast in the Clinical Trials Regulation adopted by the European Union in 2014, which allows to use data already stored beyond the end and the specific scope of a trial, with the usual strict safeguards. ESMO spokespersons stated, "We are calling upon the European Union to assure that all forms of public health research will survive and be able to function within the safeguards that are in place, without adding the nearly impossible administrative burden of re-consenting each patient, every time, for every single project, which could irreversibly slow down the accelerated pace that cancer research has gained over the past decades."



PROTEIN ANALYSIS SOFTWARE

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Defective Autophagy Triggers Type II Diabetes in Mouse Model

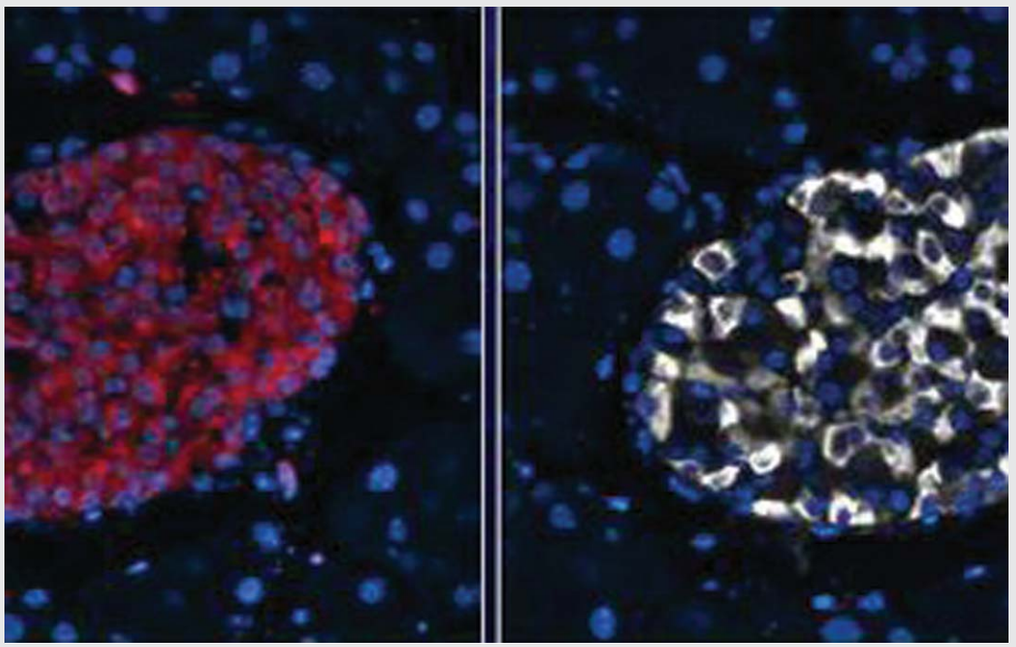
A defect in the cellular cleansing process known as autophagy in individuals with type II diabetes causes the build-up of toxic beta-cell amyloid polypeptide (IAPP or amylin), a scenario similar to the build-up of beta amyloid peptides (Abeta) in Alzheimer's disease.

Autophagy is a self-degradative cellular process that is important for balancing sources of energy at critical times in development and in response to nutrient stress. Autophagy also plays a housekeeping role in removing misfolded or aggregated proteins, clearing damaged organelles, such as mitochondria, endoplasmic reticulum and peroxisomes, as well as eliminating intracellular pathogens. Thus, autophagy is generally thought of as a survival mechanism, although its deregulation has been linked to non-apoptotic cell death. Autophagy can be either non-selective or selective in the removal of specific organelles, ribosomes and protein aggregates, although the mechanisms regulating aspects of selective autophagy are not fully understood.

Investigators at the University of California, Los Angeles (USA; www.ucla.edu) linked a defect in autophagy to the excess of IAPP seen in patients with type II diabetes. One of the defining features of type II diabetes is insulin resistance. This is a condition wherein the body is unable to utilize insulin effectively, resulting in increased insulin production. Since proinsulin and proIAPP are secreted together, this results in an increase in the production of proIAPP as well. IAPP is a 37-residue peptide hormone that plays a role in glycemic regulation by slowing gastric emptying and promoting satiety, thereby preventing postprandial spikes in blood glucose levels.

For this study the investigators created a novel mouse model that expressed autophagy defects specifically in beta-cells with expression of the human form of islet amyloid polypeptide.

Results published in the July 18, 2014, online edition of the *Journal of Clinical Investigation* revealed that mice that were hemizygous for transgenic expression of human IAPP did not develop diabetes; however, loss of beta-cell-specific autophagy in these animals induced diabetes, which was attributable to accumulation of toxic human IAPP oligomers and loss of beta-cell mass. In human IAPP-expressing mice that lacked beta-cell autophagy, increased oxidative damage and loss of an antioxidant-protective pathway appeared to contribute to increased beta-cell apoptosis. These findings indicated that autophagy/lysosomal degradation defended beta-cells against toxicity induced by the oligomerization-prone human IAPP.



"Only a few previous studies have reported that autophagy is important for beta cell function and survival," said contributing author Dr. Safia Costes, a postdoctoral researcher in endocrinology, diabetes, and hypertension at the University of California, Los Angeles. "Those studies, however, were not conducted to address the role of this process in the regulation of the amyloidogenic protein, which is an important contributor to type II diabetes. The goal of our work is to understand the cellular mechanisms responsible for beta-cell destruction so that we can identify the best targets for beta-cell protection. This would aid the development of the next generation of treatments as well as combination therapies for type II diabetes."

Results presented in the current study pinpointed similarities between type II diabetes, Alzheimer's disease, and other neurodegenerative diseases that are marked by an accumulation of toxic forms of amyloid proteins. Dr. Costes said, "This demonstrates the importance of autophagy in clearing out these harmful proteins to prevent both type II diabetes and Alzheimer's disease."

Image: A beta cell that has nonfunctioning autophagy shows increased oxidative damage (stained in red) in the pancreatic islets (shown in white) (Photo courtesy of UCLA).

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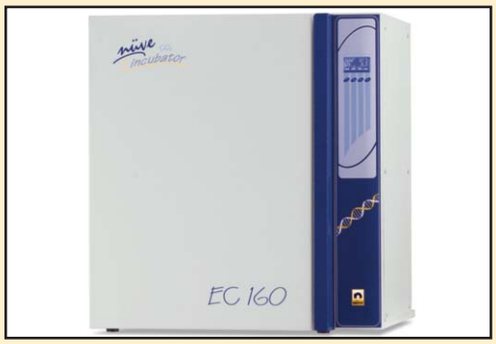

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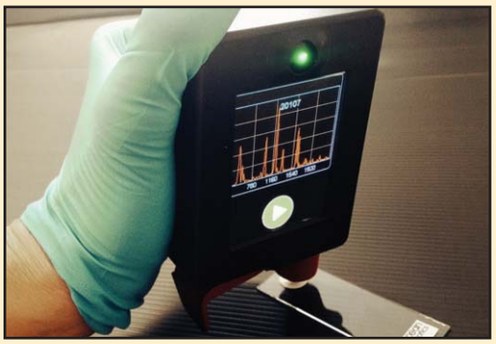

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Assessing Myeloma Progression Using Calcium Isotope Analysis

Scientists are revealing how an Earth science research principle can be used in biomedical situations to predict the development of disease.

The researchers evaluated a new approach to detecting bone loss in cancer patients by using calcium isotope analysis to predict whether myeloma patients are at risk for developing bone lesions, a key characteristic of the disease. They believe they have a potential way to chart the progression of multiple myeloma, a deadly disease that ultimately impacts a patient's bones. The technique could help customize therapies to protect bone better and also act as a way to monitor for possible disease progression or recurrence.

"Multiple myeloma is a blood cancer that can cause painful and debilitating bone lesions," said Dr. Gwyneth Gordon, an associate research scientist in Arizona State University's (ASU; Tempe, USA; www.asu.edu) School of Earth and Space Exploration, and co-lead author of the study. "We wanted to see if we could use isotope ratio analysis, a common technique in geochemistry, to detect the onset of disease progression."

"At present, there is no good way to track changes in bone balance except retrospectively using X-ray methods," said Ariel Anbar, a professor in ASU's School of Earth and Space Exploration and the department of chemistry and biochemistry. "By the time the X-rays show something the damage has been done."

"Right now, pain is usually the first indication that cancer is affecting the bones," added Dr. Rafael Fonseca, chair of the department of medicine at the Mayo Clinic (Rochester, MN, USA; www.mayoclinic.org), and a member of the research team. "If we could detect it earlier by an analysis of urine or blood in high-risk patients, it could significantly improve their care," he added.

The researchers, which include Drs. Gordon, Melanie Channon, and Prof. Anbar from ASU and Drs. Jorge Monge (co-lead author), Qing Wu, and Fonseca from Mayo Clinic, described the tests and their findings in an early on-line edition June 12, 2014, of the Nature publication *Leukemia.*

The technique measures the naturally occurring calcium isotopes that the researchers think can serve as an effective near-real-time detector of bone metabolism for multiple myeloma patients. Bone destruction in myeloma manifests itself in osteoporosis, bone lesions, and fractures. The ASU-Mayo Clinic research builds on an earlier [US] National Aeronautics and Space Administration (NASA; Houston, TX, USA; www.nasa.gov) study by the ASU team. That research focused on healthy individuals participating in an experiment. "This is the first demonstration that the technique has some ability to detect bone loss in patients with disease," said Prof. Anbar, a biogeochemist at ASU.

With the technology, bone loss is identified by carefully analyzing the isotopes of calcium that are naturally present in blood. Patients do not need to ingest any artificial tracers and are not exposed to any radiation for the test. The only harm that occurred with the new method, according to Prof. Anbar, is a pinprick for a blood draw.

The technique makes use of a fact well known to Earth scientists but not normally used in biomedicine – different isotopes of a chemical element can react at slightly different rates. The earlier NASA study showed that when bones form the lighter isotopes of calcium enter bone a little faster than the heavier isotopes. That difference, called isotope fractionation, is the key to the technology.

In healthy, active humans, bone is in "balance," meaning bone is forming at about the same rate as it dissolves (resorbs). But if bone loss is occurring, then the isotopic composition of blood becomes enriched in the lighter isotopes as bones resorb more quickly than they are formed. The effect on calcium isotopes is very small, typically less than a 0.02% change in the isotope ratio. But even effects that small can be measured by using precise mass spectrometry methods available at ASU.

With the new test, the ASU-Mayo Clinic researchers found that there was a link between how active the disease was and the change in the isotope ratios. Furthermore, the isotope ratios forecasted disease activity better than, and independent from, standard clinical variables.

Prof. Anbar noted that while the technology has worked on a small group of patients, more still needs to be done to validate initial findings and enhance the effectiveness of analysis.

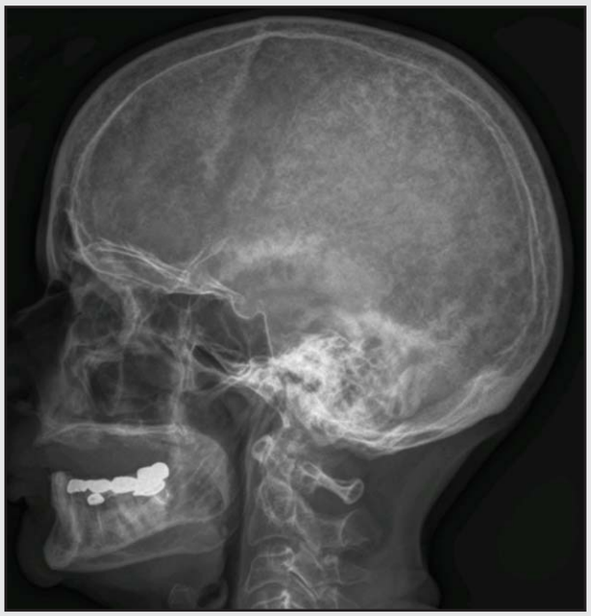

Image: X-ray of a skull. Researchers tested a new approach to detecting bone loss in cancer patients by using calcium isotope analysis to predict whether myeloma patients are at risk for developing bone lesions, a hallmark of the disease (Photo courtesy of Arizona State University / Mayo Clinic).

Biomedical Research Advanced by Technology That Sees Through Organs

The capability to see through organs and even the entire body to visualize long-range connections between cells, as well as the subtle aspects of cellular structures has been a long-time quest for biologists. A study has now made this a reality, revealing simple ways for making opaque organs, bodies, and human tissue biopsies transparent, while keeping the cellular structures and connections intact.

The protocols could create avenues for a better determination of brain-body interactions, more accurate clinical diagnoses and disease monitoring, and a new generation of therapies for disorders ranging from autism to chronic pain. "Although the idea of tissue clearing has been around for a century, to our knowledge, this is the first study to perform whole-body clearing, as opposed to first extracting and then clearing organs outside the adult body," said senior study author Dr. Viviana Gradinaru of the California Institute of Technology (Caltech; Pasadena, USA; www.caltech.edu). The findings were published July 31, 2014, in the journal *Cell.* "Our methodology has the potential to accelerate any scientific endeavor that would benefit from whole-organism mapping, including the study of how peripheral nerves and organs can profoundly affect cognition and mental processing, and vice versa."

Three-dimensional maps of intact organs and bodies are key for understanding complex, long-distance cellular interactions that play an important role in a range of biological processes. But until now, methods for making whole organs or bodies transparent and thus amenable to imaging and generating three-dimensional (3-D) maps have been limited to the brain or embryos. Dr. Gradinaru and her collaborators earlier developed a brain-clearing technique called CLARITY (Clear, Lipid-exchanged, Acrylamide-hybridized Rigid, Imaging/immunostaining compatible, Tissue hYdrogel), which involves embedding tissue into hydrogels to preserve its 3-D structure and important molecular features, and then using detergents to extract lipids that make the tissue opaque.

In the new study, the researchers set out to make CLARITY suitable for whole organs and bodies, in part by making the process faster. First, they identified the optimal hydrogel that allows detergents to quickly remove lipids from tissue using an approach named passive CLARITY technique (PACT). To great speed up the clearing process without causing tissue damage, they introduced an advanced procedure called perfusion-assisted agent release in situ (PARS), which involves directly delivering the hydrogel and clearing reagents into the bloodstream of intact rodents. The reagents diffused throughout the tissues and fully clarified organs such as the kidney, heart, lung, and intestine within two to three days, while the whole brain and entire body cleared within two weeks.

The researchers also developed a recipe for refractive index matching solution (RIMS), which enables the long-term storage of cleared tissue and imaging thick, cleared tissue using a traditional confocal microscope. The new technologies allow for the study of intact connections between cells as well as structures and molecules within single cells using standard genetic and molecular biology techniques.

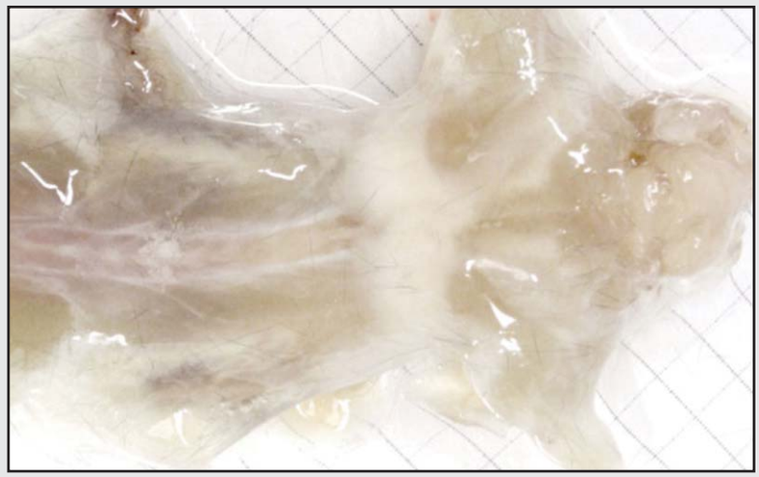

Image: A mouse has been rendered transparent by a technique called CLARITY that involves a water-based gel and detergents (Photo courtesy of the California Institute of Technology).

New Reaction Vessel Heating System Is Cleaner and Safer

Biotech and other life science researchers can create a safer, cleaner, and more efficient working environment in their laboratories by switching from oil bath-based heating of reaction vessels to a new, high-performance reaction block that can be used with any hotplate stirrer.

The Asynt (Isleham, United Kingdom; www.asynt.com) DrySyn MULTI converts any standard hotplate stirrer into a high performance reaction block accommodating three round-bottomed flasks (10 to 500 milliliters) or up to 12 reaction tubes or vials.

DrySyn MULTI heating blocks, which are made of chemically resistant, anodized aluminum, offer excellent heating performance to over 300 degrees Celsius. They are able to heat a reaction flask faster than an oil bath with less energy consumption and without the inherent risks and mess of an oil bath. The DrySyn MULT system is based on an ingenious three-way clamp that secures flasks in place. Furthermore, DrySyn MULTI's shallow well shape increases reaction visibility and minimizes the possibility of glass failure.

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Research Lab to Develop World's First Neural Device to Restore Memory

A USD 2.5 million grant has been awarded to a US research lab to develop an implantable neural device with the ability to record and stimulate neurons within the brain to help restore memory.

The US Department of Defense's Defense Advanced Research Projects Agency (DARPA) awarded the grant to Lawrence Livermore National Laboratory (LLNL; Livermore, CA, USA; www.llnl.gov). The research builds on the knowledge that memory is a process in which neurons in specific regions of the brain encode information, store it, and retrieve it. Specific types of disorders and injuries, including traumatic brain injury (TBI), Alzheimer's disease, and epilepsy, disrupt this process and cause memory loss. TBI, specifically, has affected 270,000 military service members since 2000.

The objective of LLNL's research initiated by LLNL's Neural Technology group and undertaken in collaboration with the University of California, Los Angeles (UCLA; USA; www.ucla.edu) and Medtronic (Minneapolis, MN, USA; www.medtronic.com) is to develop a device that uses real-time recording and closed-loop stimulation of neural tissues to bridge gaps in the injured brain and restore individuals' ability to form new memories and access previously formed ones.

The research is funded by DARPA's Restoring Active Memory (RAM) program. Specifically, the neural technology group are trying to develop a neuromodulation system, an advanced electronics system to modulate neurons, which will investigate areas of the brain associated with memory to understand how new memories are formed. The device will be developed at LLNL's Center for Bioengineering.

"Currently, there is no effective treatment for memory loss resulting from conditions like TBI," said LLNL's project leader Dr. Satinderpall Pannu, director of the LLNL's Center for Bioengineering, a unique facility dedicated to fabricating biocompatible neural interfaces. "This is a tremendous opportunity from DARPA to leverage Lawrence Livermore's advanced capabilities to develop cutting-edge medical devices that will change the health care landscape."

LLNL engineers will devise a miniature, wireless and chronically implantable neural device that will incorporate both single neuron and local field potential recordings into a closed-loop system to implant into TBI patients' brains. The device implanted into the entorhinal cortex and hippocampus will allow for stimulation and recording from 64 channels located on two high-density electrode arrays. The entorhinal cortex and hippocampus are brain regions associated with memory.

The arrays will connect to an implantable electronics bundle capable of wireless data and power telemetry. An external electronic system worn around the ear will store digital information associated with memory storage and retrieval and provide power telemetry to the implantable package using a custom radiofrequency (RF) coil system.

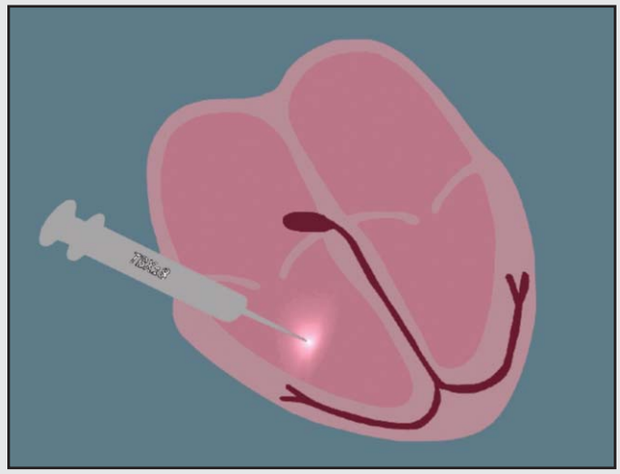
The device's electrodes will be integrated with electronics using advanced LLNL integration and 3-D packaging technologies, and are designed to last throughout the duration of treatment. The microelectrodes that are the heart of this device are embedded in a biocompatible, flexible polymer. Using the Center for Bioengineering's capabilities, Dr. Pannu and his team of engineers have achieved 25 patents and many publications during the last 10 years. The team's goal is to build the new prototype device for clinical testing by 2017.

Lawrence Livermore's collaborators, UCLA and Medtronic, will focus on conducting clinical trials and creating parts and components, respectively. "The RAM program poses a formidable challenge reaching across multiple disciplines from basic brain research to medicine, computing and engineering," said Itzhak Fried, lead investigator for the UCLA on this project and professor of neurosurgery and psychiatry and biobehavioral sciences at the David Geffen School of Medicine at UCLA and the Semel Institute for Neuroscience and Human Behavior.

LLNL's work on the Restoring Active Memory program supports President Obama's Brain Research through Advancing Innovative Neurotechnologies (BRAIN) initiative. "Our years of experience developing implantable microdevices, through projects funded by the Department of Energy [DOE], prepared us to respond to DARPA's challenge," said Lawrence Livermore engineer Kedar Shah, a project leader in the neural technology group.

Image: Engineer Kedar Shah works on a neural device at the Lab's Center for Micro- and Nanotechnology (Photo courtesy of the Lawrence Livermore National Laboratory).

Gene Therapy Induces Functional Pacemaker Cells in Pig Heart-Failure Model



Cardiovascular disease researchers working with a porcine heart failure model have demonstrated the practicality of using gene therapy to replace implanted electronic pacemakers to regulate heartbeat.

Investigators at Cedars-Sinai Heart Institute (Los Angeles, CA, USA; www.csmc.edu) examined whether adenoviral-TBX18 gene transfer could create biological pacemaker activity in vivo in a large-animal model of complete heart block. The Tbx18 gene is required for development of pacemaker cells in the heart during fetal development but is normally not functional after birth.

Tbx18 gene therapy is aimed at treating a group of arrhythmias known as sick sinus syndrome. In a healthy heart, sinoatrial (SA) nodal cells act as the heart's pacemaker and cause the heart to beat in a regular rhythm. While SA nodal cells comprise only about 10 thousand of the 10 billion cells in the heart, they play a crucial role in the heart's function. In sick sinus syndrome the SA node does not function properly and causes irregular heartbeat. Currently the treatment for sick sinus syndrome is to remove the SA nodal cells that are not functioning properly and to implant an electronic pacemaker to maintain a regular rhythm. However, currently used electronic pacemakers have drawbacks such as equipment malfunction, limited battery life, lack of nervous system regulation, and risks associated with implantation of the device in one's chest.

The investigators reported in the July 16, 2014, online edition of the journal *Science Translational Medicine* that functional SA nodal cells, which could be identified by their distinctive morphology, were found at the site of adenovirus-TBX18 injection shortly after intramyocardial injection of the material. Biological pacemaker activity was evident in the TBX18-transduced animals starting at day two and persisted for the duration of the study (14 days) with minimal backup electronic pacemaker use. No local or systemic safety concerns arose during the course of the study.

"We have been able, for the first time, to create a biological pacemaker using minimally invasive methods and to show that the biological pacemaker supports the demands of daily life," said senior author Dr. Eduardo Marbán, director of the Cedars-Sinai Heart Institute. "We also are the first to reprogram a heart cell in a living animal in order to effectively cure a disease. Originally, we thought that biological pacemaker cells could be a temporary bridge therapy for patients who had an infection in the implanted pacemaker area. These results show us that with more research, we might be able to develop a long-lasting biological treatment for patients."

The investigators hope that continued success with animal studies will lead to human clinical trials in about three years.

Image: Scientists are creating a biological pacemaker, by injecting a gene into the hearts of sick pigs that changed ordinary cardiac cells into a special kind that induce a steady heartbeat. The study is one step toward developing an alternative to electronic pacemakers that are implanted into 300,000 Americans a year (Photo courtesy of Science / AAAS).

Evolutionary Changes Reproduced in the Lab by Manipulating Embryonic Development of Mice

Researchers have been able experimentally to reproduce in mice morphologic alterations that have taken millions of years to occur. Through small and gradual modifications in the embryonic development of mice teeth, produced in the laboratory, scientists have obtained teeth that morphologically are very similar to those observed in the fossil registry of rodent species that evolved from mice millions of years ago.

To modify the development of their teeth, the team from the Institute of Biotechnology of the University of Helsinki (Finland; www.biocenter.helsinki.fi) worked with embryonic teeth cultures from mice not coded by the ectodysplasin A (EDA) protein, which regulates the formation of structures and differentiation of organs in the embryo throughout its development. The teeth obtained with these cultures which present this mutation develop into very fundamental forms, with very uniform crowns. Scientists gradually added different amounts of the EDA protein to the embryonic cells and let them develop.

The researchers observed that the teeth formed with different levels of complexity in their crown. The more primitive changes observed coincide with those which took place in animals of the Triassic period, some two hundred million years ago. The development of more posterior patterns corresponds with the different stages of evolution discovered in rodents that already became extinct in the Paleocene Epoch, approximately 60 million years ago. Researchers have therefore achieved the reproduction of the transitions observed in the fossil registry of mammal teeth.

The scientists were able to compare the shape of these teeth with a computer-generated prediction model created by Dr. Isaac Salazar-Ciudad, researcher at the Universitat Autònoma de Barcelona (UAB; Spain; www.uab.cat) and at the University of Helsinki, which reproduces how the tooth changes from a group of equal cells to a complicated three-dimensional (3-D) structure, with the full shape of a molar tooth, computing the position of space of each cell. The model is capable of forecasting the changes in the morphology of the tooth when a gene is engineered, and therefore offers an explanation of the processes that cause these specific alterations to occur in the shape of teeth throughout evolution.

"Evolution has been explained as the ability of individuals to adapt to their environment in different ways," Dr. Salazar-Ciudad stated, "But we do not know why or how individuals differ morphologically. The research helps to understand evolution, in each generation, as a game between the possible variations in form and natural selection."

The research findings were published July 30, 2014, in the journal *Nature*.

White-Matter Deficits Found in Codeine-Containing Cough Syrup Users

A magnetic resonance imaging (MRI) study of chronic users of codeine-containing cough syrups (CCS) has found deficits in specific regions of brain white matter and linked these changes with increased impulsivity in codeine-containing cough syrup users. These findings were consistent with findings from earlier research of heroin and cocaine addicts. White matter disruptions also correlated with the duration of CCS use.

Researchers used MR diffusion tensor imaging (DTI), combined with fractional anisotropy, to study the white matter integrity of chronic CCS users. Deficits were discovered in multiple regions of the brain, including the inferior fronto-occipital fasciculus, which other studies have found to be abnormal in other forms of addiction, such as addiction to the Internet, alcohol, and heroin. The researchers, from the department of medical imaging of the First Affiliated Hospital of Gannan Medical University (Ganzhou, China; www.gmu.cn), and the departments of medical imaging and interventional radiology, Cancer Center, Sun Yat-Sen University (Guangzhou, China), reported that the white matter deficits in CCS users also correlated with increased impulsivity characteristics in the study subjects, as measured by the Barratt impulsiveness scale. These findings were consistent with the findings of earlier studies of heroin and cocaine addicts. White matter disruptions also correlated with the duration of CCS use.

Codeine-containing cough syrups have become one of the most widespread drugs of abuse in young people worldwide. Progressive alterations in the white matter of users' brains may cause greater impulsivity in CCS users. The study's findings were published August 2014 on the website of the *American Journal of Neuroradiology (AJNR)*.

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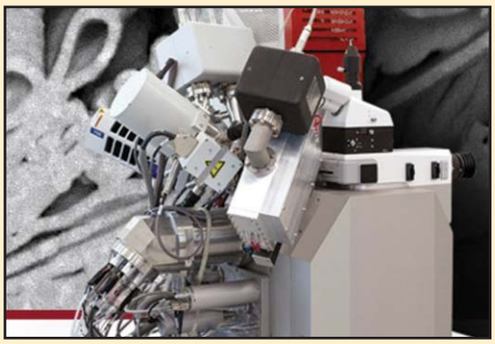

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GENE ANALYZER
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Vision Scientific

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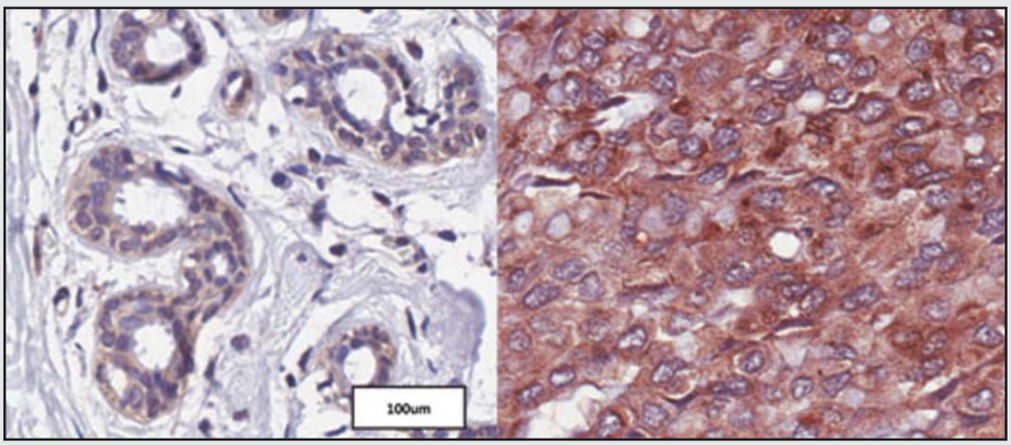
DP103 Cited as Breast Cancer Biomarker And Potential Treatment Target

Cancer researchers in Singapore have identified the DP103 oncogene in human breast cancers as a biomarker for the molecular processes that drive reappearance and metastasis of tumors following chemotherapy.

The 824-amino acid DEAD-box protein DP103 belongs to the family of DExD/H-box proteins, named after the signature Asp-Glu-Ala-Asp/His motif within the helicase domain (Gemin3, DDX20). DP103 was originally cloned and characterized as a component of the splicing machinery in concert with SMN, Sm, and other Gemin proteins.

Investigators at ASTAR's Institute of Molecular and Cell Biology (Singapore; www.a-star.edu.sg) and at the National University of Singapore's Cancer Science Institute (www.csi.nus.edu.sg) have identified DP103 as a biomarker and metastasis-driving oncogene in human breast cancers. Furthermore, they determined that DP103 elevated matrix metallopeptidase 9 (MMP9) levels, which are associated with metastasis and invasion through activation of NF-kappaB.

The NF-kappaB family of transcription factors comprises five structurally related proteins that form homo- and heterodimers through their highly conserved DNA binding/dimerization Rel homology domain. Binding of NF-kappaB to IkappaB proteins maintains NF-kappaB in an inactive state. Activation of NF-kappaB in normal cells is inducible and is a tightly controlled event. Upon stimulation, IkappaBs are phosphorylated by the IkappaB kinase (IKK) complex (consisting of IKK1, IKK2, and NEMO proteins). IkappaB phosphorylation leads to its rapid proteolysis, thereby allowing NF-kappaB to function as a transcription factor.



Reduction of DP103 expression in invasive breast cancer cells reduced phosphorylation of IKK2, abolished NF-kappaB–mediated MMP9 expression, and impeded metastasis in a mouse xenograft model. In breast cancer patient tissues, elevated levels of DP103 correlated with enhanced MMP9, reduced overall survival, and reduced survival after relapse.

Together, these findings, which were published in the August 1, 2014, online edition of the *Journal of Clinical Investigation*, indicated that a positive DP103/NF-kappaB feedback loop promoted continual NF-kappaB activation in invasive breast cancers and activation of this pathway was linked to cancer progression and the acquisition of chemotherapy resistance. Thus, DP103 also has potential as a therapeutic target for breast cancer treatment.

"DP103 is a novel biomarker that could help doctors select appropriate treatments for breast cancer patients at an early stage. It is also a therapeutic target which could be explored further to develop drugs that suppress breast cancer growth, as well as metastasis," said contributing author Dr. Alan Kumar, assistant professor of pharmacology at the National University of Singapore.

"Doctors are unable to tell if a breast cancer patient will respond to chemotherapy until six months after the treatment has been prescribed. It is very worrisome as the ones who are not responsive to chemotherapy usually also suffer relapses due to metastasis. This DP103 gene that we found explains the link and will facilitate doctors in selecting suitable treatments for different cases of breast cancer," said senior author Dr. Vinay Tergaonkar, an associate professor at the Institute of Molecular and Cell Biology.

Image: The difference in DP103 (red) levels in a healthy person (left) and a breast cancer patient (right) (Photo courtesy of the National University of Singapore's Cancer Science Institute).

Loss of Regulatory Enzyme Spurs Kidney Cancer Growth

Cancer researchers have found that the enzyme fructose-1,6-bisphosphatase 1 (FBP1) is missing or inactive in the clear cell renal cell carcinoma (ccRCC) form of kidney cancer, a lack that gives the cancer cells a metabolic advantage over surrounding normal tissue.

FBP1 is a gluconeogenesis regulatory enzyme that catalyzes the hydrolysis of fructose1,6-bisphosphate to fructose 6-phosphate and inorganic phosphate. Fructose-1,6-diphosphatase deficiency is associated with hypoglycemia and metabolic acidosis.

Investigators at the University of Pennsylvania (Philadelphia, USA; www.upenn.edu) have been working with a mouse ccRCC model. Previous studies had shown that kidney tumors of this type were characterized by elevated glycogen levels and fat deposition. Development of these characteristics was associated with elevated expression of hypoxia inducible factors (HIFs) and mutations in the von Hippel-Lindau (VHL) encoded protein, pVHL, which occurs in 90% of ccRCC tumors.

The VHL protein (pVHL) is involved in the regulation of hypoxia inducible factor 1 alpha (HIF1alpha). This is a subunit of a heterodimeric transcription factor that at normal cellular oxygen levels is highly regulated. Under normal physiological conditions, pVHL recognizes and binds to HIF1alpha only when oxygen is present due to the post translational hydroxylation of two proline residues within the HIF1alpha protein. pVHL is an E3 ligase that ubiquitinates HIF1alpha and causes its degradation by the proteasome. In low oxygen conditions or in cases of VHL disease where the VHL gene is mutated, pVHL does not bind to HIF1alpha. This allows the subunit to dimerize with HIF1beta and activate the transcription of a number of genes, including vascular endothelial growth factor, platelet-derived growth factor B, erythropoietin, and genes involved in glucose uptake and metabolism.

In the current study, which was published in the July 20, 2014, online edition of the journal *Nature*, the investigators used an integrative approach comprising metabolomic profiling and metabolic gene set analysis to examine more than 600 kidney tumors from human patients. They determined that FBP1 was uniformly depleted in all of the ccRCC tumors examined. The human FBP1 locus was found to reside on chromosome 9q22, the loss of which was associated with poor prognosis for ccRCC patients.

FBP1 was found in the nucleus of normal cells, where it bound to HIF to modulate its effects on tumor growth. In cells lacking FBPI, rapidly growing tumor cells were found to produce energy up to 200 times faster than normal cells.

"This study is the first stop in this line of research for coming up with a personalized approach for people with clear cell renal cell carcinoma-related mutations," said senior author Dr. Celeste Simon, professor of cell and developmental biology at the University of Pennsylvania. "Since FBP1 activity is also lost in liver cancer, which is quite prevalent, FBP1 depletion may be generally applicable to a number of human cancers."

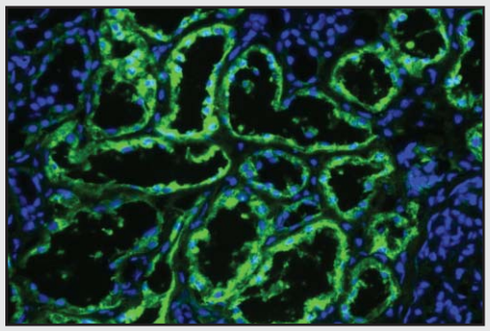


Image: A metabolic enzyme has an unexpected role in regulating gene expression in kidney cancer. Image of primary human kidney tissue: FBP1 protein (green); cell nuclei (blue) (Photo courtesy of Bo Li and Brian Keith, Perelman School of Medicine, University of Pennsylvania).

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REAL-TIME PCR SYSTEM
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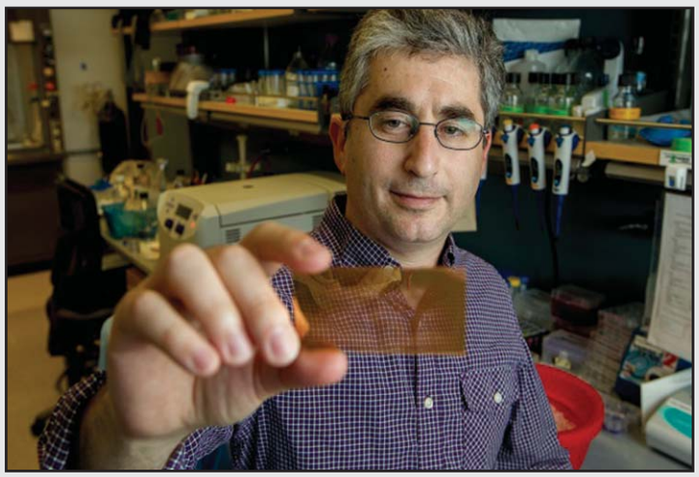
Microchip Invented for Faster, Simpler Type-1 Diabetes Diagnosis, Risk Assessment, and Biomarker Discovery

Researchers have succeeded in developing a low-cost, portable, nanotech microchip-based test for diagnosing type-1 diabetes that would speed diagnosis and screening, and enable new approaches to studying how the disease develops.

The type-1 diabetes (T1D) microchip test was invented by a Stanford University (Stanford, CA, USA; www.stanford.edu) team led by Stanford University School of Medicine's Brian Feldman, MD, PhD, assistant professor of pediatric endocrinology, the Bechtel Endowed Faculty Scholar in Pediatric Translational Medicine, and pediatric endocrinologist at Lucile Packard Children's Hospital Stanford. It distinguishes between the two main forms of diabetes mellitus – T1D, being an autoimmune disease, has auto-antibodies not present with type-2 diabetes (T2D). Until now, making the distinction has required a slow, expensive test available only in sophisticated health-care settings. The new handheld, inexpensive test can be performed outside hospital settings and could improve patient care worldwide; including satisfying a global need in many parts of the world where the old test is prohibitively expensive and difficult to perform. The researchers are seeking US Food and Drug Administration (FDA) approval of the device.

The old, slow test detects the auto-antibodies using radioactive materials, takes several days, can only be performed by highly-trained lab staff, and costs several hundred dollars per patient. In contrast, the new, relatively low-cost microchip method uses no radioactivity, produces results in minutes, and requires minimal training to perform. And each chip, expected to cost about USD 20 to produce, can be used for upward of 15 tests. The microchip also uses a much smaller volume of blood than the older test: instead of a lab-based blood draw it can be done with blood from a finger prick.

"With the new test, not only do we anticipate being able to diagnose diabetes more efficiently and more broadly, we will also understand diabetes better – both the natural history and how new therapies impact the body," said Prof. Feldman. Better testing is also needed as recent changes in who gets T1D vs. T2D have made it risky to categorize patients based on their age, ethnicity, or weight, as was common in the past due to the sharp distinctions that no longer exist. A cheap handheld test in the doctor's office would help prevent adult patients from undergoing damaging incorrect treatment due to having been misdiagnosed with T2D. Also, there is growing evidence that early, aggressive new therapies of T1D improves patients' long-term prognoses, possibly via halting the autoimmune attack on the pancreas and preserving some of the body's ability to make insulin.



In addition to new diabetics, people who are at risk of developing T1D, such patients' close relatives, may also benefit as the test will allow doctors to quickly and cheaply track their auto-antibody levels before onset of symptoms. Furthermore, because of its low cost, the test may allow the first broad screening for T1D auto-antibodies to identify those at risk in the population at large. The test would also facilitate testing for volunteers in programs such as "TrialNet," the nationwide USA study that monitors risk of relatives of T1D patients.

"The auto-antibodies truly are a crystal ball," said Prof. Feldman, "Even if you don't have diabetes yet, if you have one auto-antibody linked to diabetes in your blood, you are at significant risk; with multiple auto-antibodies, it's more than 90% risk." "There is great potential to capture people before they develop the disease," added Prof. Feldman, "But the old test was prohibitive for that type of thinking because it was so costly and time-consuming."

The microchip, a plasmonic chip, relies on fluorescence-based antibody detection. The team's innovation is that the glass plates forming the base of each microchip are coated with an array of nanoparticle-sized islands of gold, which intensify the fluorescent signal, enabling reliable antibody detection. The test was validated using blood samples from people newly diagnosed with diabetes and from people without diabetes. Blood samples from both groups were tested with both the old test and the microchip-based test.

The study, by Zhang B, Kumar RB, Honjie D, and Feldman BJ, was described in the journal *Nature Medicine*, July 13, 2014, (online ahead of print).

Image: Dr. Brian Feldman holding one of the microchips designed for diagnosing type-1 diabetes (Photo courtesy of Stanford University School of Medicine, Office of Communication & Public Affairs).

Experimental Drug Kills Cancer Cells by Interfering with Their Ion Transport Mechanism

An experimental anticancer drug induces cells to enter a molecular pathway leading to apoptosis by skewing their ion transport systems to greatly favor the influx of chloride anions. To promote development of low molecular weight ion transporter drugs, investigators at The University of Texas, Austin (USA; www.utexas.edu) sought to show that there was a direct correlation between a change in cellular chloride anion concentration and cytotoxicity for synthetic ion carriers.

To accomplish this goal, the investigators and their colleagues from five other research institutes created two synthetic ion transporters – pyridine diamide-strapped calix[4]pyrroles – that bind to chloride ions.

Results published in the August 11, 2014, online edition of the journal *Nature Chemistry* revealed that these compounds induced coupled chloride anion and sodium cation transport in both liposomal models and cells, and promoted cell death by increasing intracellular chloride and sodium ion concentrations. Removing either ion from the extracellular media or blocking natural sodium channels prevented this effect.

"We have demonstrated that this mechanism is viable, that this idea that has been around for over two decades is scientifically valid, and that is exciting," said contributing author Dr. Jonathan L. Sessler, professor of chemistry at the University of Texas, Austin. "We were able to show sodium is really going in, chloride is really going in. There is now, I think, very little ambiguity as to the validity of this two-decades-old hypothesis. We have shown that this mechanism of chloride influx into the cell by a synthetic transporter does indeed trigger apoptosis. This is exciting because it points the way towards a new approach to anticancer drug development."

The synthetic molecules described in the current study induce programmed cell death in both cancerous and healthy cells. To be of any value in treating cancer, a version of a chloride anion transporter will have to be developed that acts only on cancer cells.

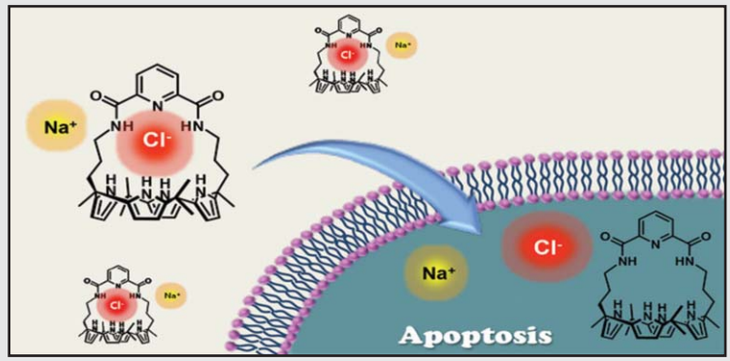


Image: A diagram showing how synthetic ion transporters can induce apoptosis by facilitating chloride anion transport into cells (Photo courtesy of University of Texas at Austin).

Tool Library Application Helps Neuroscientists Interpret Big Data

New technologies for tracking brain activity are generating extraordinary quantities of information. This data may contain new clues into how the brain works, but only if researchers can interpret it. To help make sense of the data, neuroscientists can now exploit the power of distributed computing with Thunder, a library of tools.

In an age of "big data," a single computer cannot always find the solution that a user requires. Instead, computational tasks must be distributed across a collection of computers that analyze a massive data set together. It is how Facebook and Google extract an individuals' web history to present them with targeted ads, and how Amazon and Netflix recommend a favorite book or movie; however, big data is about more than only marketing.

Thunder was developed at the Howard Hughes Medical Institute's (HHMI) Janelia Research Campus (Ashburn, VA, USA; http://janelia.org) and the application speeds the analysis of data sets that are so enormous and complex they would take days or weeks to analyze on a single workstation – if a single workstation could do it at all. Janelia group leaders Drs. Jeremy Freeman, Misha Ahrens, and other colleagues at Janelia and the University of California, Berkeley (USA; www.berkeley.edu), reported in the July 27, 2014, issue of the journal *Nature Methods* that they have used Thunder to quickly find patterns in high-resolution images collected from the brains of active zebrafish and mice with multiple imaging techniques.

Significantly, they have employed Thunder to analyze imaging data from a new microscope that Ahrens and colleagues developed to monitor the activity of nearly every individual cell in the brain of a zebrafish as it behaves in response to visual stimuli. That technology is described in a companion paper published in the same issue of *Nature Methods*.

Thunder can run on a private cluster or on Amazon's cloud computing services. Researchers can find everything they need to begin using the open source library of tools at http://freeman-lab.github.io/thunder.

New microscopes are capturing images of the brain faster, with better spatial resolution, and across wider regions of the brain than ever before. However, all these aspects come encrypted in gigabytes or even terabytes of data. On a single workstation, simple calculations can take hours. "For a lot of these data sets, a single machine is just not going to cut it," Dr. Freeman noted.

It is not just the sheer volume of data that exceeds the limits of a single computer, the investigators noted, but also its complexity. "When you record information from the brain, you don't know the best way to get the information that you need out of it. Every data set is different. You have ideas, but whether or not they generate insights is an open question until you actually apply them," said Dr. Ahrens.

Distributed computing can accelerate analysis while exploring the full richness of a data set, but many alternatives are available. Dr. Freeman decided to build on a new platform called Spark. Developed at the University of California, Berkeley's AMPLab, Spark is rapidly becoming a favored tool for large-scale computing across industry. Spark's capabilities for data caching eliminates the logjam of loading a complete data set for all but the first step, making it well-suited for interactive, exploratory analysis, and for complex algorithms requiring repeated operations on the same data. Furthermore, Spark's well designed and versatile application programming interfaces (APIs) help simplify development. Thunder uses the Python API, which Dr. Freeman hopes will make it particularly easy for others to adopt, given Python's increasing use in neuroscience and data science.

To make Spark suitable for analyzing a broad range of neuroscience data, Dr. Freeman first developed standardized representations of data that were amenable to distributed computing. He then worked to express typical neuroscience workflows into the computational language of Spark. From there, the biologic questions that he and his colleagues were curious about drove development.

Using the application, the investigators analyzed images of the brain in minutes, interacting with and revising analyses without the lengthy delays associated with previous methods. In images taken of a mouse brain with a two-photon microscope, for example, the researchers found cells in the brain whose activity varied with running speed. For analyzing much larger data sets, tools such as Thunder are not just helpful, they are vital, according to the scientists. This is true for the information gathered by the new microscope that the investigators developed for tracking whole-brain activity in response to visual stimuli.

In 2013, Drs. Ahrens and Janelia group leader Dr. Phillip Keller used high-speed light-sheet imaging to engineer a microscope that captures neuronal activity cell by cell across nearly the entire brain of an immature zebrafish. That microscope produced amazing images of neurons in the zebrafish brain firing while the fish was inactive. However, Dr. Ahrens wanted to use the technology to study the brain's activity in more complex situations. Now, the scientists have combined their original technology with a virtual-reality swim simulator that Dr. Ahrens previously developed to provide fish with visual feedback that simulates movement.

Combining these two technologies lets Dr. Ahrens monitor activity throughout the brain as a fish modifies its behavior based on the sensory data it receives. The technique generates approximately a terabyte of data per hour – presenting a data analysis challenge that helped motivate the development of Thunder. When Drs. Freeman and Ahrens applied their new tools to the data, patterns quickly emerged. As examples, they identified cells whose activity was tied to movement in particular directions and cells that fired specifically when the fish was at rest, and were able to characterize the dynamics of those cells' activities. Example analyses such as these, and example data sets, are available at http://research.janelia.org/zebrafish.

Dr. Ahrens now plans to investigate more complex questions using the new technology, and both he and Dr. Freeman foresee expansion of Thunder. "At every level, this is really just the beginning," Dr. Freeman stated.

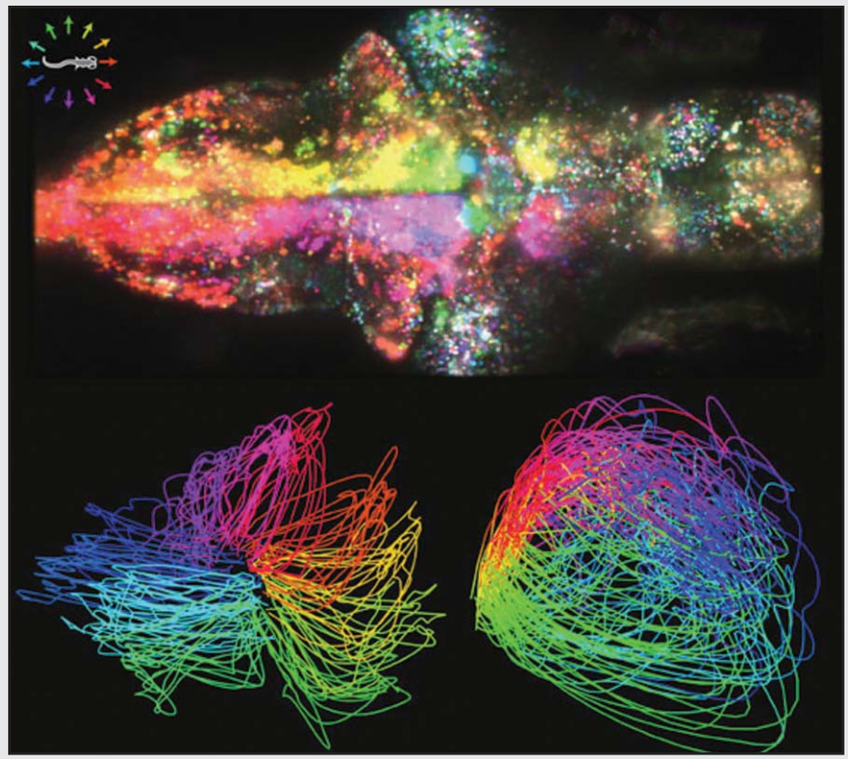


Image: On the top: a whole-brain map of direction selectivity. Every neural response has been colored based on the direction of a moving visual stimulus for which the response was largest. Bottom: low-dimensional embeddings of whole-brain dynamics. Each trace represents how activity across the brain evolves following the presentation of a single stimulus. On the bottom: color indicates the direction of the stimulus (left), whereas on the right color indicates the passage of time (Photo courtesy of Dr. Jeremy Freeman, University of California, Berkeley).

Germany's Merck to Buy Sigma-Aldrich for USD 17 Billion

cont'd from cover

Karl-Ludwig Kley, chairman of Merck KGaA (Darmstadt, Germany; www.merck.de) called the deal a "quantum leap" for the company's life science business, whose contributions to the German firm's overall earnings would more than double with the addition of Sigma-Aldrich (St. Louis, MO, USA; www.sigmaaldrich.com). "In one of the world's key industries two companies that fit perfectly together have found each other to present a much broader product offering to our global customers in research, pharma, and biopharma manufacturing, and diagnostic and testing labs." He added that the deal "will secure stable growth and profitability in an industry that is driven by trends, such as the globalization of research and manufacturing. What's more, the combination gives us the possibility to invest even more in innovation going forward."

Sigma-Aldrich president and CEO Rakesh Sachdev said that the combined firms "will be well-positioned to deliver significant customer benefits, including a broader, complementary range of products and capabilities, greater investment in breakthrough innovations, enhanced customer service, and a leading e-commerce and distribution platform in the industry."

Sigma-Aldrich develops and manufactures a wide range of life science products, including chemicals, biochemicals, and equipment for life science research – including studies directed at genomic and proteomic research – as well as biotech and pharma development. The company was founded in 1951 and has about 9,000 employees.

American and European Partners Establish a Microscopy Center of Excellence

A prominent American university has announced a partnership agreement with a major European producer of microscopes and imaging tools that will establish a center for the use of cutting-edge imaging technologies and the development of new ones. The West Campus of Yale University (New Haven, CT, USA; www.yale.edu) is the site of the new Leica Microsystems (Wetzlar, Germany; www.leica-microsystems.com) Center of Excellence. This center will provide researches with access to cutting-edge imaging tools to resolve sub-cellular structures and other targets of interest. At the same time, Leica Microsystems will gain access to world-class investigators and the latest developments in research applications. This relationship will afford Yale researchers access to expert technical and applications support, along with instrumentation, which Leica Microsystems will continuously update with the latest technology. In addition, Yale and Leica Microsystems will collaborate in the development of novel imaging technologies.

"We are extremely excited to embark on this journey of discovery with Yale University as our first such partnership in the USA," said Doug Reed, general manager of Leica Microsystems North America. "This cooperation will provide some of the best scientific minds access to imaging tools previously out of reach, plus allow Leica Microsystems ready access to new ideas from outstanding scientific leaders, which will be used to guide development of tomorrow's innovations."

"It is electrifying to see our two organizations establish this world-class resource. Not only is this partnership aligned with our mission at West Campus of advancing research through innovative collaboration, it also ensures that current top-flight imaging technology is always within reach to all at Yale," said Dr. Christopher Incarvito, director of research operations & technology at Yale University's West Campus.

The Center of Excellence is scheduled to be formally dedicated during opening ceremonies on October 20–21, 2014. These two days will feature scientific, applications and technology talks, round table discussions, and a keynote address from Dr. Joerg Bewersdorf, associate professor of cell biology and biomedical engineering at the Yale School of Medicine. Leica Microsystems will also host a super-resolution workshop with free access and sample preparation through October 31, 2014.

"This is just the beginning of what we feel will be a long and discovery-filled relationship between Leica Microsystems and Yale," said Doug Reed, "we cannot wait to get started and invite all interested scientists to attend!"

Market for Proteomics Research Tools Facing Sharp Growth Trend

A report recently released to the biotech industry predicts sharp growth in research efforts in the field of proteomics with concurrent growth in sales of research supplies and equipment.

The report, "Proteomics Markets for Research and IVD Applications," which was prepared by Kalorama Information (New York, NY, USA; www.kaloramainformation.com), indicated that the USD 5 billion market for proteomics instruments, reagents, and testing for research and diagnostic applications was likely to grow rapidly over the next several years, despite cost pressures generally in research.

Proteomics is the study of protein structure and function. At the cellular level, investigators attempt to determine which proteins are expressed, when and where they are expressed, what is their structure in both active and inactive states, what roles they play in the life of the cell, and how they interact with other proteins and molecules.

While many different types of technologies are used to study proteins, demands for the three main technologies: mass spectrometry, antibodies (or antibody capture), and knowledge bases are expected to grow significantly.

"It is enormously difficult to study proteins, but hard-fought discoveries made in the research enable biomarker discovery, drug discovery, new IVDs, and personalized solutions," said Bruce Carlson, publisher of Kalorama Information. "There are many manufacturers willing to assist customers with technologies, creating a vibrant market. New platforms based on a wide range of proteomics technologies have already started to reach the in vitro diagnostics market. The major question today is not whether or not these novel platforms and biomarkers will emerge as a significant market opportunity in the IVD market, but when. How long will it take for companies to obtain the required regulatory approvals? How long will it take for the tests to penetrate these markets? The answers to this question will vary with individual platforms and assays, and will depend on factors such as the unmet need, how well the new platform and assays meet that need, costs, etc."

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Medica 2014. Nov 12-15; Dusseldorf, Germany; Web: www.medica-tradefair.com

India Lab Expo 2014. Nov 21-13; Hyderabad, India; Web: www.indial-abexpo.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

JANUARY 2015

MedLab 2015. Jan 26-29; Dubai, UAE; Web: www.arabhealthonline.com

FEBRUARY 2015

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

Drug Discovery Technology World Asia. Mar 23-26; Singapore; Web: www.terrapinn.com

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

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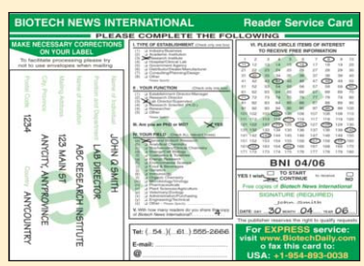

Experimental Biology 2015. Mar 28-Apr 1; Boston, MA, USA; Web: http://experimentalbiology.org

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

Society for General Microbiology Annual Conference 2015. Mar 30-Apr 2; Birmingham, UK; Web: www.sgm.ac.uk

APRIL 2015

SEACARE 2015 – 18th Southeast-Asian Healthcare & Pharma Show. Apr 6-8; Kuala Lumpur, Malaysia; Web: http://abcex.com/default.aspx

Bio Process International – European Conference and Exhibition. Apr 14-15; Düsseldorf, Germany; Web: www.informa-ls.com/event/Bpi2014

Analitika 2015. Apr 14-17; Moscow, Russia; Web: www.analitikaexpo.com

MAY 2015

Biomarkers & Diagnostics World Congress 2015. May 5-7; Philadelphia, PA, USA; Web: www.biomarker-worldcongress.com

ANALYTICA 2016. May 10-13; Munich, Germany; Web: www.analytica.de

BIOtech 2015 Japan. May 13-15; Tokyo, Japan; Web: www.bio-t.jp

ISLH 2015 – International Symposium on Technological Innovations in Laboratory Hematology. May 19-21; Chicago, IL; Web: www.islh.org

HOSPITALAR 2015. May 19-22; Sao Paulo, Brazil; Web: www.hospitalar.com

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BIO International 2015. Jun 15-18; Philadelphia, PA, USA; Web: http://convention.bio.org

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AUGUST 2015

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SEPTEMBER 2015

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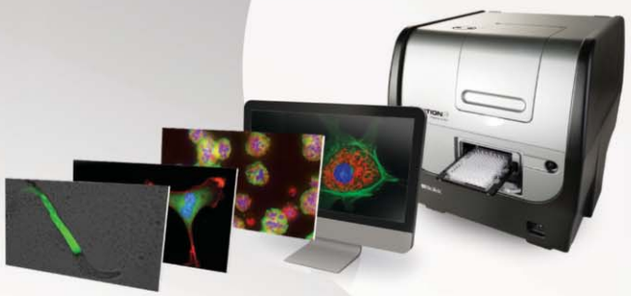

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