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Bio Research INTERNATIONAL

Novel Algorithms Enable Automated Monitoring of Cell-to-Cell Interactions

A novel combination of microscopy, time-lapse video recording, and analytical algorithms enables tracking of individual cell-to-cell interactions, which will boost research towards cancer immunotherapy treatments.

The technique, Time-lapse Imaging Microscopy in Nanowell Grids (TIMING) was developed by investigators at the University of Houston (TX, USA; www.houston.edu) and their colleagues at the University of Texas M.D. Anderson Cancer Center (www.mdanderson.org). Studies using this method were carried out using fluorescently labeled human T-cells, natural killer cells (NK), and various target cells (NALM6, K562, EL4), which

Cont'd on page 4

Intein-Based Protein Splicing Generates Molecular Sensors

Researchers have used intein-based protein splicing to generate synthetic protein components that are able to detect specific DNA sequences and subsequently trigger a desired intracellular response such as activation of a gene or initiation of a molecular pathway.

An intein is a segment of a protein that is able to excise itself and join the remaining portions (the exteins) with a peptide bond in a process termed protein splicing. Intein-mediated protein splicing occurs after the intein-containing mRNA has been translated into a protein. This precursor protein contains three segments – an N-extein followed by the intein

Cont'd on page 4

New Computer Models Show How Tumors Evolve

Cancer researchers are using innovative computer models to create 3D simulations of tumors developing over time, in order to explain why the tumor mass is almost exclusively composed of one type of cell while a similar mass of normal tissue would be composed of many cell types.

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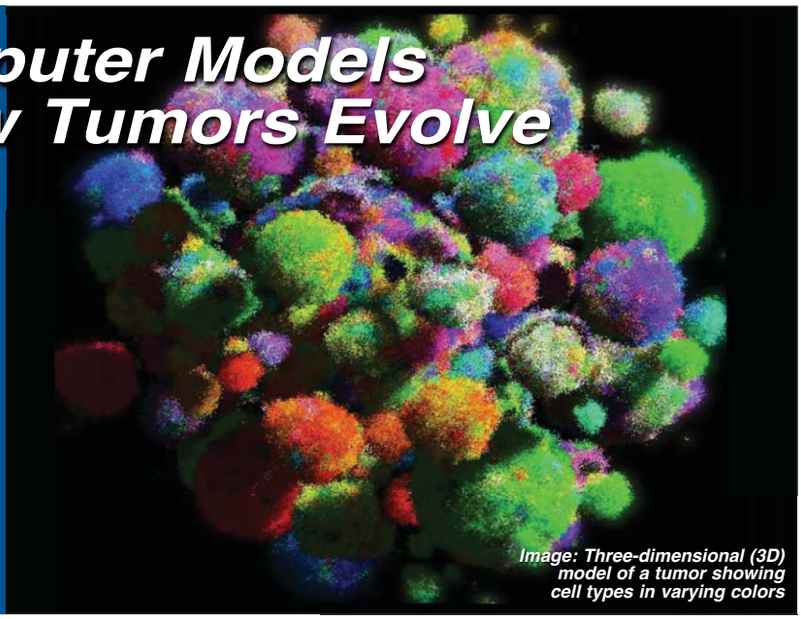

Image: Three-dimensional (3D) model of a tumor showing cell types in varying colors

Image: Courtesy of Dr. Bartlomiej Waclaw and Dr. Martin A. Nowak, the University of Edinburgh

Method Improves RNA Isolation from Exonomes

A novel spin column-based method has been developed that provides a faster, more reliable means for the isolation of RNA from exosomes for research, delivering high-quality results with less labor-intensive sample preparation.

Exosomes and other extracellular vesicles (commonly referred to as EVs) have generated considerable attention for their potential applications in both diagnostics and therapeutics. The contents of these vesicles are the subject of intense research, and the relatively recent discovery of RNA inside EVs has raised interest in the biological function

Cont'd on page 3

Pipette Automator Prevents Repetitive Strain Injuries

A powerful pipetting accessory makes life easier for technicians in both clinical and research laboratories. Prolonged and repetitive pipetting sessions bear the risk of strain and fatigue, often resulting in

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Custom-Designed SNP Array Facilitates Population Genomic Studies

Japanese genomic researchers have created a single nucleotide polymorphism (SNP) array optimized for studies on the Japanese population.

The so-called "Japonica Array" was designed by investigators at the Tohoku University Tohoku Medical Megabank Organization (Sendai, Japan; www.megabank.tohoku.ac.jp). As source material, the investigators used the Tohoku Medical Megabank Organization's reference panel (referred to as the 1KJPN panel), which contains more than 20 million SNPs from whole-genome sequence data from 1070 Japanese individuals. The panel contains the largest number of haplotypes of Japanese ancestry to date.

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INSIDE

Latest Advances & Applications in:

OLYMPUS

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Method Improves RNA Isolation from Exonomes

Image: The exoRNeasy serum/plasma kits for efficient purification of RNA from exosomes and other extracellular vesicles in serum or plasma samples (Photo courtesy of QIAGEN).

cont'd from cover

of these RNAs as well as their potential as biomarkers for cancer and other diseases. Traditional ultracentrifugation-based protocols to isolate EVs are labor-intensive and subject to significant variability. The traditional ultracentrifugation method for isolating EV RNA is now being superseded by a series of spin column-based extraction kits developed by QIAGEN (Venlo, The Netherlands; www.qiagen.com) in conjunction with Exosome Diagnostics, Inc. (Cambridge, MA, USA; www.exosomedx.com) and marketed by QIAGEN under the name exoEasy (for whole EV isolation) and exoRNeasy (for extraction of EV RNA).

Use of the exoRNeasy kit was described in a paper in the August 28, 2015, online edition of the journal *PLOS ONE* that was authored by investigators from QIAGEN and Exosome Diagnostics. Briefly, pre-filtered plasma was mixed with binding buffer and added to the exoEasy membrane affinity column to bind the EVs to the membrane. After centrifugation, the flow-through was discarded, and wash buffer was added to the column to remove nonspecifically retained material. After another centrifugation and discarding of the flow-through, the vesicles were lysed by adding QIAzol to the spin column, and the lysate was collected by centrifugation. The miRNeasy Serum/Plasma Spike-In Control was added. Following addition of chloroform, thorough mixing, and centrifugation to separate organic and aqueous phases, the aqueous phase was recovered and mixed with ethanol. The sample-ethanol mixture was added to an RNeasy MinElute spin column and centrifuged. The column was washed three times with buffer followed by elution of RNA in water. This procedure allowed concentrating the extracellular RNA from four milliliters of plasma or serum into a final volume of 14 microliters of water. This method was an improvement over traditional methods in providing a faster, more standardized way to achieve reliable high quality RNA preparations from EVs in serum and plasma.

"The QIAGEN exoRNeasy Maxi Kit standardized protocol, developed in partnership with Exosome Diagnostics, Inc., is the most sophisticated method for the extraction of RNA from exosomes," said contributing author Dr. Markus Sprenger-Haussels, head of the sample technologies unit at QIAGEN. "The study also reinforces QIAGEN's leadership for sample technologies which are paving the way for the growing acceptance of liquid biopsies. QIAGEN provides a range of novel sample technologies for liquid biopsies to help gain valuable molecular insights from easily collected samples of blood or other liquids."

"As the world leader in sample preparation, QIAGEN's partnership with Exosome Diagnostics is accelerating the pace at which researchers and drug developers across the globe are utilizing exosomes from biofluids. Exosomes provide a powerful molecular research approach that is getting significant attention given its many advantages over tissue-based approaches," said Dr. Johan Skog, CSO of Exosome Diagnostics. "Our ongoing collaboration with QIAGEN and these important new data provide further validation that Exosome Diagnostics' technology offers a highly sensitive and reproducible method to isolate and extract nucleic acid from exosomes for routine laboratory use."

Novel Algorithms Enable Automated Monitoring of Cell-to-Cell Interactions

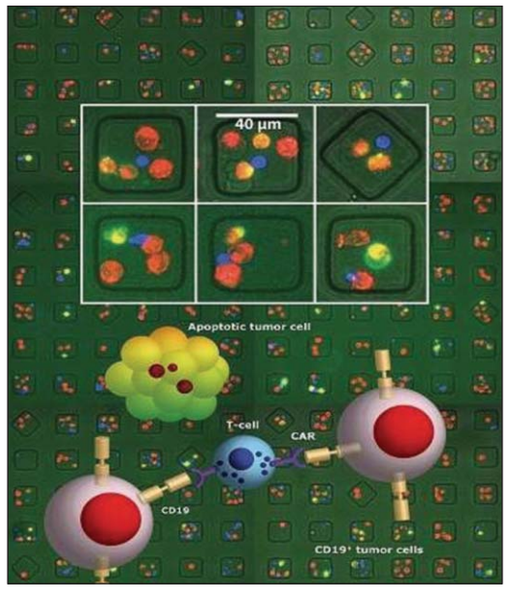
cont'd from cover

were co-incubated on polydimethylsiloxane nanowell arrays and imaged using multichannel time-lapse microscopy. Novel cell segmentation and tracking algorithms accounted for cell variability and exploited the nanowell confinement property to increase the yield of correctly analyzed nanowells from 45% (existing algorithms) to 98% for wells containing one effector and a single target, enabling automated quantification of cell locations, morphologies, movements, interactions, and deaths without the need for manual proofreading.

Automated analysis of recordings from 12 different experiments published in the June 9, 2015, online edition of the journal *Bioinformatics* demonstrated automated nanowell delineation accuracy greater than 99%, automated cell segmentation accuracy greater than 95%, and automated cell tracking accuracy of 90%, with default parameters, despite variations in illumination, staining, imaging noise, cell morphology, and cell clustering.

Example analysis revealed that NK cells efficiently discriminated between live and dead targets by altering the duration of conjugation. The data also demonstrated that cytotoxic cells displayed higher motility than non-killers, both before and during contact.

"We have developed a game-changing piece of software that can accurately analyze an entire grid of nanowell videos and make quantitative measurements," said senior author Dr. Badri Roysam, professor of electrical and computer engineering at the University of Houston. "It is essentially the combination of a supermicroßßscope and a supercomputer to screen cell-cell interactions on a large scale.



The proposed algorithms dramatically improved the yield and accuracy of the automated analysis to a level at which the automatically generated cellular measurements can be utilized for biological studies directly, with little/no editing."

Image: Researchers used time-lapse imaging microscopy in nanowell grids (TIMING) to demonstrate that CD4+ CD19-chimeric antigen receptor (CAR+) T-cells participate in multi-killing of tumor cells with slower kinetics of killing than CD8+CAR+T cells but high motility subgroups of both T-cell subsets have similar kinetics (Photo courtesy of the University of Houston).

Intein-Based Protein Splicing Generates Molecular Sensors

cont'd from cover

followed by a C-extein. After splicing has taken place, the resulting protein contains the N-extein linked to the C-extein; this splicing product is also termed an extein. Pharmaceutical inhibition of intein excision may be a useful tool for drug development; the protein that contains the intein will not carry out its normal function if the intein does not excise, since its structure will be disrupted.

Investigators at the Massachusetts Institute of Technology (Cambridge, USA; www.mit.edu) exploited the programmability of zinc-finger DNA recognition to drive the intein-mediated splicing of an artificial trans-activator that signaled to a genetic circuit containing a given reporter or response gene. The zinc finger proteins (each containing a separate intein) were engineered to recognize adjacent DNA sequences within the targeted gene. Thus, when the sequences were aligned, the inteins meshed and were excised, allowing the extein halves to rejoin and form a functional protein.

In the September 21, 2015, online edition of the journal *Nature Methods* the investigators described the use of these protein sensors to mediate sequence recognition-induced apoptosis as well as to detect and report a viral infection.

This approach established a synthetic biology framework for endowing mammalian cells with sentinel capabilities, which provided a programmable means to detect and remove infected cells. It may also be used to identify positively transduced or transfected cells, isolate recipients of intentional genomic edits, and increase the repertoire of inducible parts in synthetic biology.

"There is a range of applications for which this could be important," said senior author Dr. James Collins, professor of medical engineering and science at the Massachusetts Institute of Technology. "This allows you to readily design constructs that enable a programmed cell to both detect DNA and act on that detection, with a report system and/or a respond system."

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Custom-Designed SNP Array Facilitates Population Genomic Studies

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Beginning with the 1KJPN panel, the investigators designed a novel custom-made SNP array, containing 659,253 SNPs, including tag SNPs for imputation, SNPs of Y- chromosome and mitochondria, and SNPs related to previously reported genome-wide association studies and pharmacogenomics.

The Japonica Array was found to provide better imputation performance for Japanese individuals than the existing commercially available SNP arrays. Imputation is an information science technique for estimating the genotype of several millions of unmeasured SNPs with a SNP array by combining it with a reference panel.

The genomic coverage of the Japonica Array was 96.9% for common SNPs; that is, almost all common SNPs were covered by this array. Furthermore, the coverage of low-frequency SNPs reached 67.2%, which was higher than those of other existing arrays.

The investigators confirmed the high quality genotyping performance of the Japonica array using the 288 samples from the 1KJPN reference panel. Results obtained from genotype screening with a high-throughput sequencer yielded an average call rate of 99.7% and an average concordance rate of 99.7%. Thus, the creation of custom-made SNP arrays based on a population-specific reference panel was shown to be a practical way to facilitate further association studies through genome-wide genotype imputations.

The study was published in the June 25, 2015, online edition of the *Journal of Human Genetics*.

Image: The "Japonica Array" contains 659,253 SNPs, including tag SNPs for imputation, SNPs of Y chromosome and mitochondria, and SNPs related to previously reported genome-wide association studies and pharmacogenomics (Photo courtesy of Tohoku Medical Megabank Organization).

New Computer Models Show How Tumors Evolve

Cancer researchers used computer modeling to create three-dimensional simulations of tumors developing over time in order to explain why the tumor mass is almost exclusively composed of one type of cell while a similar mass of normal tissue would be composed of many cell types.

Most cancers in humans are large, measuring centimeters in diameter, and composed of many billions of cells. An equivalent mass of normal cells would be highly heterogeneous as a result of the mutations that occur during each cell division. What is remarkable about cancers is that virtually every cell within a large tumor often contains the same core set of genetic alterations, with heterogeneity confined to mutations that emerge late during tumor growth. How such alterations expand within the spatially constrained three-dimensional architecture of a tumor, and come to dominate a large, pre-existing lesion, has been unclear.

An international team of investigators from the University of Edinburgh (United Kingdom; www.ed.ac.uk), Harvard University (Cambridge, MA, USA; www.harvard.edu), and Johns Hopkins University (Baltimore, MD, USA; www.jhu.edu) developed computer models to describe how short-range dispersal and cell turnover could account for rapid cell mixing inside the tumor during its evolution.

The investigators reported in the August 26, 2015, online edition of the journal *Nature* that a small selective advantage of a single cell within a large tumor would allow the descendants of that cell to replace the precursor mass in a clinically relevant time frame.

The investigators stated that their model not only provided insights into spatial and temporal aspects of tumor growth, but also suggested that targeting short-range cellular migratory activity could have marked effects on tumor growth rates.

First author Dr. Bartlomiej Waclaw, a researcher in the school of physics and astronomy at the University of Edinburgh, said, "Computer modeling of cancer enables us to gain valuable insight into how this complex disease develops over time and in three dimensions."

Researchers Pinpoint Binding Site For Clostridium Difficile Binary Toxin

A team of molecular microbiologists has located the site where the bacterium *Clostridium difficile*'s binary toxin binds to intestinal cells' LSR (lipolysis-stimulated lipoprotein receptor) protein and triggers a mechanism that results in the invasion of the host cells by the bacteria.

Clostridium difficile is a serious intestinal pathogen that can cause severe diarrhea and life-threatening intestinal infections especially after long-term treatment with antibiotics. The bacteria produce the binary, actin ADP-ribosylating toxin CDT (*Clostridium difficile* transferase). While CDT can lead to death of the host cells through collapse of the actin cytoskeleton, low doses of CDT result in the formation of microtubule-based protrusions on the cell surface that increase the adherence and colonization of *C. difficile*.

Investigators at the University of Freiburg (Germany; www.uni-freiburg.de) examined how CDT binds to its host cell LSR. They reported in the April 16, 2015, online edition of the *Journal of Biological Chemistry* that CDT interacted with the extracellular, Ig-like domain of LSR with an affinity in the nanomolar range. They identified LSR splice variants in the colon carcinoma cell line HCT116 and disrupted the LSR gene in these cells by applying CRISPR-Cas9 technology.

CRISPRs (clustered regularly interspaced short palindromic repeats) are segments of prokaryotic DNA containing short repetitions of base sequences. Each repetition is followed by short segments of "spacer DNA" from previous exposures to a bacterial virus or plasmid. CRISPRs are found in approximately 40% of sequenced bacteria genomes and 90% of sequenced archaea. CRISPRs are often associated with cas genes that code for proteins related to CRISPRs. The CRISPR/Cas complex comprises a prokaryotic immune system that confers resistance to foreign genetic elements such as plasmids and phages and provides a form of acquired immunity. Since 2013, the CRISPR/Cas system has been used in research for gene editing (adding, disrupting, or changing the sequence of specific genes) and gene regulation. By delivering the Cas9 protein and appropriate guide RNAs into a cell, the organism's genome can be cut at any desired location.

LSR segments created by the CRISPR/Cas technique were expressed ectopically in cells lacking the LSR gene. Results of these experiments showed that intracellular parts of LSR were not essential for plasma membrane targeting of the receptor and cellular uptake of CDT. Furthermore, by generating a series of N- and C-terminal truncations of the binding component of CDT (CDTb), they found that amino acids 757 to 866 of CDTb were sufficient for binding to LSR.

"In the future, it should be possible to block these areas in the toxin and receptor in order to prevent the toxin from entering the host cell," said senior author Dr. Panagiotis Papatheodorou, professor of biology at the University of Freiburg.

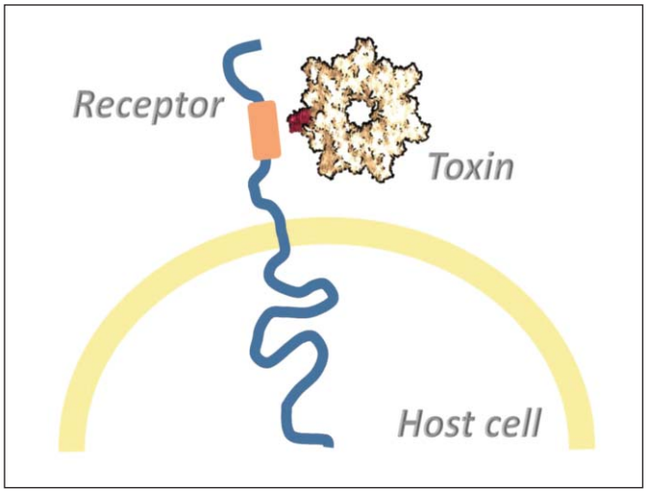

Image: Bacterial toxins usually exert their full deadly effect in the host cell's interior. The toxins overcome the cell membrane by binding to a surface receptor, which conveys them into the cell's interior (Photo courtesy of Dr. Panagiotis Papatheodorou, University of Freiburg).

Low-Calorie Cranberry Juice Shown to Lower Cardiovascular Risk

Supplementing the diet with low-calorie cranberry juice (LCCJ) reduces the chances of developing cardiovascular disease by lowering several risk factors including circulating triglycerides (TGs), C-reactive protein (CRP), glucose, and diastolic blood pressure (BP).

Investigators at the United States Department of Agriculture (Beltsville, MD, USA; www.usda.gov) and Ocean Spray Cranberries, Inc. (Lakeville-Middleborough, MA, USA; www.oceanspray.com) conducted a double blind, placebo-controlled, parallel-arm study on 30 women and 26 men. For eight weeks the participants ate controlled diets supplemented with twice daily drinks of 240 milliliters of LCCJ or a placebo beverage, containing 173 or 62 mg of phenolic compounds and 6.5 or 7.5 g of total sugar per 240 milliliter serving, respectively.

Results published in the April 22, 2015, online edition of the *Journal of Nutrition* revealed that fasting serum TGs were lower after consuming LCCJ and that the participants with higher baseline TG concentrations were more likely to experience a larger treatment effect. Other cardiovascular disease risk factors including serum C-reactive protein (CRP), diastolic blood pressure (BP), and fasting plasma glucose were lower for individuals consuming LCCJ than for individuals consuming the placebo beverage. Furthermore, LCCJ had a beneficial effect on homeostasis model assessment of insulin resistance for participants with high baseline values.

"At the start and end of the experiment, the researchers measured things like blood pressure, blood sugar levels, blood lipids, as well as C-reactive protein, a marker of inflammation," said contributing author Dr. Christina Khoo, director of research sciences at Ocean Spray Cranberries, Inc. "All of these measurements come together to tell a story. The worse off these numbers are in an individual, the more likely he or she will face a health condition like diabetes, heart disease, or stroke in the future. These findings suggest that polyphenols help to protect our bodies, and may be adept at keeping a large number of ailments at bay. Luckily for us, a rich source of polyphenols is only a glass of cranberry juice away. Among the commonly consumed fruits in our diets, cranberries boast some of the highest levels of polyphenols – more than apples, blueberries, grapes, or cherries."

The investigators suggested that individuals drinking two glasses of LCCJ per day could experience up to a 10% percent lower risk of heart disease and a 15% percent lower risk of stroke.

Pipette Automator Prevents Repetitive Strain Injuries

cont'd from cover

repetitive strain injuries (RSI) and less reproducible results. INTEGRA Biosciences (Zizers, Switzerland; www.integra-biosciences.com) has a solution to this problem, the VIAFLO Assist. This instrument automates operation of their line of VIAFLO II electronic pipettes to safeguard users from RSI and to increase the reproducibility of prolonged pipetting protocols such as serial dilutions, plate filling, and reagent addition.

The VIAFLO Assist boasts a touch wheel interface with full color screen that offers rapid menu navigation. The operator accesses menus and settings by simply moving a finger over the touch wheel.

Any VIAFLO II multichannel pipette can be attached to the VIAFLO Assist pipette adapter. Pipettes are available as 8-, 12-, and 16-channel models, covering a volume range of 0.5 –1,250 microliters. The instrument accommodates 6-well to 384-well microtiter plates in either landscape or portrait orientation and delivers reagents from one of three (10 milliliter, 25 milliliter, or 100 milliliter) reagent reservoirs.

The instrument has a small footprint and is lightweight, making it easy to relocate at any time and facilitates its use in a laminar flow cabinet. The pipette is ergonomically friendly, and the fact that it connects to the VIAFLO Assist by Bluetooth means fewer wires on the benchtop.

Dr. Danielle Stephens, manager of the Forsyth Institute's (Cambridge, MA, USA; www.forsyth.org) Luminex Core facility, praised the pipetting accessory when she said, "The VIAFLO Assist is an excellent tool for a high throughput laboratory looking to increase efficiency and precision to reach a higher capacity."

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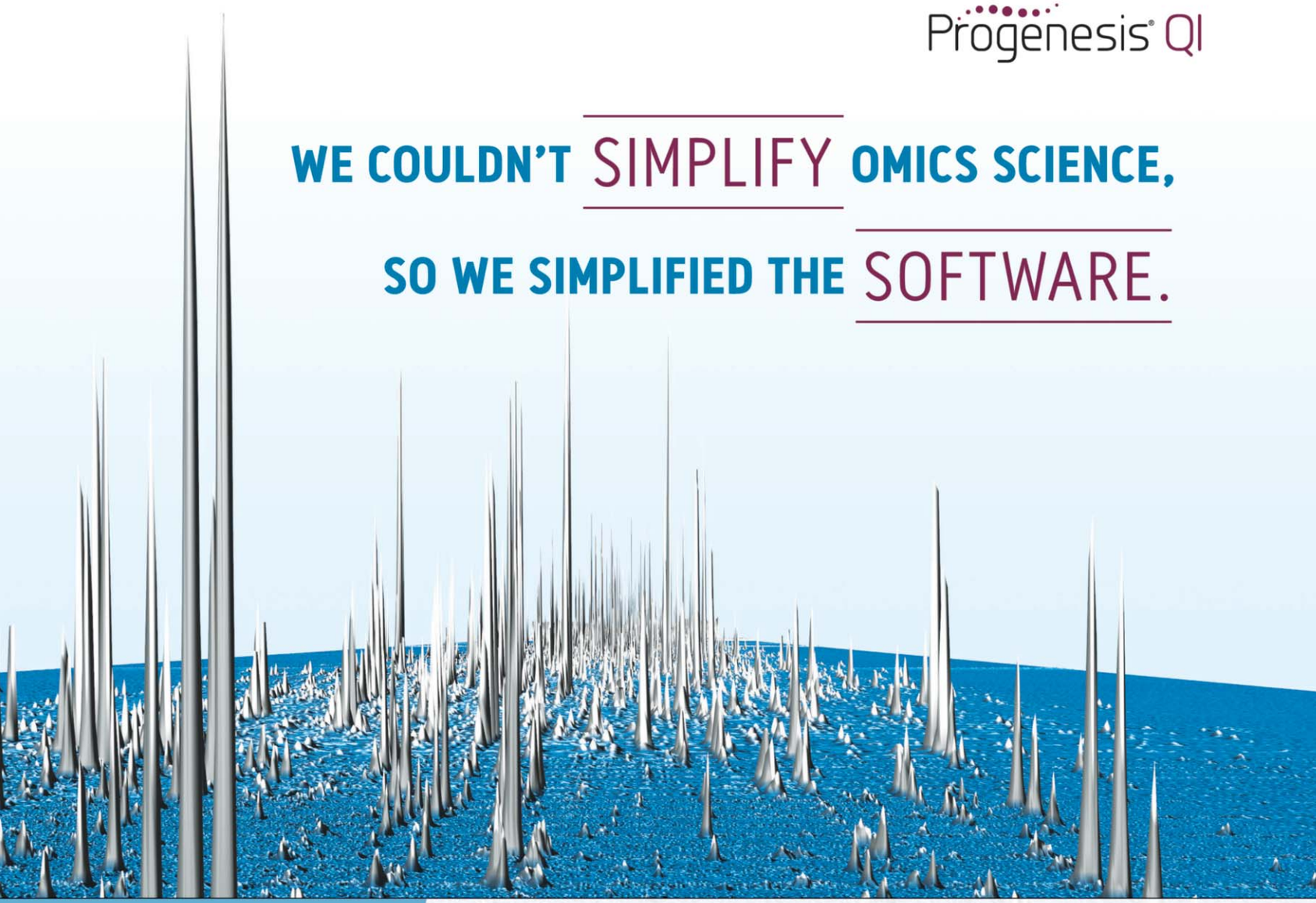

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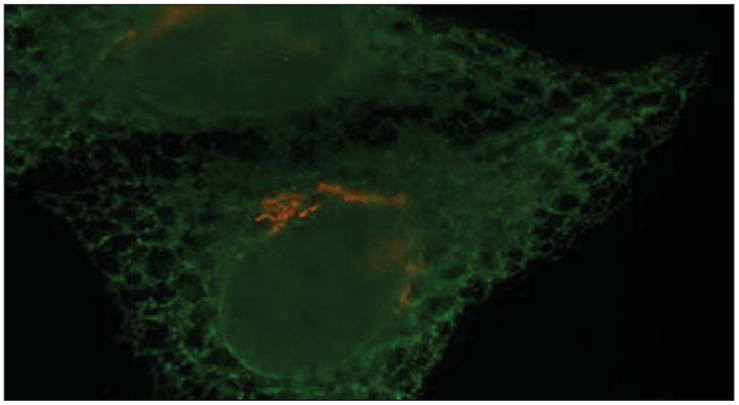
Extracellular Protein Kinase Interacts with Broad Spectrum of Potential Substrates

A single enzyme, Fam20C (family with sequence similarity 20, member C), has been linked to the phosphorylation of more than 100 different proteins representing nearly 90% of all phosphorylated secreted proteins.

Fam20C is a Golgi localized serine kinase that phosphorylates both casein and other highly acidic proteins and members of the small integrin-binding ligand, the N-linked glycoproteins family at the target motif serine-X-glucosamine.

Investigators at the University of California, San Diego (USA; www.ucsd.edu) utilized CRISPR/Cas9 gene editing as well as mass spectrometry and biochemical techniques to learn more about the role of Fam20C.

CRISPRs (clustered regularly interspaced short palindromic repeats) are segments of prokaryotic DNA containing short repetitions of base sequences. Each repetition is followed by short segments of "spacer DNA" from previous exposures to a bacterial virus or plasmid. CRISPRs are found in approximately 40% of sequenced bacteria genomes and 90% of sequenced archaea. CRISPRs are often associated with cas genes that code for proteins related to CRISPRs. The CRISPR/Cas complex comprises a prokaryotic immune system that confers resistance to foreign genetic elements such as plasmids and phages and provides a form of acquired immunity. Since 2013, the CRISPR/Cas system has been used in research for gene editing (adding, disrupting, or changing the sequence of specific genes) and gene regulation. By delivering the Cas9 protein and appropriate guide RNAs into a cell, the organism's genome can be cut at any desired location.



The investigators reported in the June 18, 2015, online edition of the journal *Cell* that use of the CRISPR/Cas system had allowed them to identify more than 100 secreted phosphoproteins as genuine Fam20C substrates. Further, they showed that Fam20C exhibited broader substrate specificity than previously thought. Appreciation of the functional rationale of Fam20C substrates suggested roles for the kinase beyond biomineralization, including lipid homeostasis, wound healing, and cell migration and adhesion.

"Nearly 60 years of protein phosphorylation research has uncovered many important functions for phosphorylation of proteins inside the cell, so there is no reason to believe these mechanisms will be any different for phosphorylation of proteins outside the cell," said first author Dr. Sandra Wiley, a staff research associate at the University of California, San Diego. "We are now investigating the biological function and importance of each protein phosphorylated by Fam20C."

Image: Cells stained orange to illuminate the endoplasmic reticulum and Golgi apparatus, the parts of the cell where the enzyme Fam20C might phosphorylate other proteins (Photo courtesy of University of California, San Diego).

New Gel Extends Release Half-Life of PEGylated Drugs

Researchers have developed a first-of-its-kind hydrogel for more effective long-term drug delivery that would also reduce side effects and discomfort for patients. Their proof-of-concept study showed effectiveness of the hydrogel with the hepatitis C drug PEGylated-interferon.

The team of researchers, led by Dr. Motoichi Kurisawa, principal research scientist at the Institute of Bioengineering and Nanotechnology (IBN; Singapore; www.ibn.a-star.edu.sg) of Singapore's Agency for Science, Technology and Research (ASTAR; www.a-star.edu.sg), developed a hydrogel that enables burst-free sustained-release of PEGylated protein drugs. "The new gel from IBN prevents premature drug release in the body. This allows for long-term drug delivery and reduces the side effects from frequent drug administration. We hope that our solution can improve the treatment and well-being of patients suffering from chronic diseases such as hepatitis C," said Prof. Jackie Y. Ying, IBN executive director.

Standard treatment for chronic hepatitis C infections includes weekly injection of PEGylated interferon. The frequent injections increase patient discomfort, are time-consuming, and can cause depression and fatigue. It has not been possible to use hydrogels to deliver drugs with long-term efficacy because controlling the drug release rate is difficult. Most hydrogels have a porous structure that causes the encapsulated drugs to leak prematurely and be eliminated rapidly from the body.

The team found a way to regulate the release rate and duration by creating a gel with 3D microscopic structures of the polymer polyethylene glycol (PEG). The microstructures function like "reservoirs" for PEGylated drugs because of the presence of PEG on the drug. This property prevents premature leaking. The drugs will also flow in and out of the many reservoirs in the gel before being released into the body. This property helps slow the drug diffusion rate. Duration of drug action can also be controlled by changing the size of the reservoir microstructures.

The study showed that a one-time administration of the hydrogel containing the PEGylated interferon was as effective as 8 injections of the medication alone, and that drug effect can last up to 2 months. The hydrogels will degrade naturally and be eliminated from the body once the drugs are fully released.

"Our hydrogels can significantly extend the half-life of hepatitis C drugs by up to 10 times longer than current treatment," said Dr. Kurisawa, "This work improves the therapeutic efficiency of the drugs, while reducing the need for frequent injections." "I believe that our method can pave the way for more effective and safe treatment of hepatitis C. We are also testing the microstructured gel for the treatment of other chronic diseases besides hepatitis C," added Dr Kurisawa.

The study, by Bae KH et al., was published online ahead of print June 11, 2015, in the journal *Biomaterials*.

Liquid Nanolaser Technology Used for Lab-on-a-Chip Diagnostic Applications

Improvements in nanoscale laser technology enable biotechnology researchers to envisage the use of such a device as the focal point for "lab on a chip" diagnostic applications.

Investigators at Northwestern University (Evanston, IL, USA; www.northwestern.edu) described an approach to achieve real-time, tunable lattice plasmon laser capability in the April 20, 2015, online edition of the journal *Nature Communications*. Their tunable liquid-based laser was constructed from arrays of gold nanoparticles and liquid gain materials.

Optically pumped arrays of gold nanoparticles surrounded by liquid dye molecules exhibited lasing emission that could be tuned as a function of the dielectric environment. Wavelength-dependent time-resolved experiments showed distinct lifetime characteristics below and above the lasing threshold. By integrating gold nanoparticle arrays within microfluidic channels and flowing in liquid gain materials with different refractive indices, the investigators achieved dynamic tuning of the plasmon lasing wavelength.

Nanoscale lasers can be mass-produced with emission wavelengths over the entire gain bandwidth of the dye employed. Thus, the same gold nanoparticle array can exhibit lasing wavelengths that can be tuned over 50 nanometers, from 860 to 910 nanometers, simply by changing the solvent used to dissolve the dye.

"Our study allows us to think about new laser designs and what could be possible if they could actually be made," said Dr. Teri W. Odom, professor of chemistry at Northwestern University. "My lab likes to go after new materials, new structures, and new ways of putting them together to achieve things not yet imagined. We believe this work represents a conceptual and practical engineering advance for on-demand, reversible control of light from nanoscopic sources."

Research on Zebrafish Embryos Reveals Origin of the Lymphatic System

A team of developmental biologists working with a zebrafish embryo model system has located the site of origin of the lymphatic system and identified a gene critical to the differentiation of stem cells into mature lymphatic cells.

Investigators at the Weizmann Institute of Science (Rehovot, Israel; www.weizmann.ac.il) exploited the transparent bodies of zebrafish embryos to document development in real time over a period of several days. By reversing the direction of the video images, they were able to determine that the cells giving rise to lymphatic vessels always originated in a niche of angioblasts localized at the same part of the embryo's major vein.

Zooming in to the molecular level, the investigators identified the Wnt5b protein as a novel lymphatic inductive signal in the zebrafish embryos and further showed that it promoted the "angioblast-to-lymphatic" transition in human embryonic stem cells as well. Wnt5b in humans is encoded by the WNT5B (Wingless-type MMTV integration site family, member 5B) gene. The WNT gene family consists of structurally related genes that encode secreted signaling proteins. These proteins have been implicated in oncogenesis and in several developmental processes, including regulation of cell fate and patterning during embryogenesis.

Writing in the May 20, 2015, online edition of the journal *Nature*, the investigators reported that addition of Wnt5b to cultures of human embryonic stem cells induced those cells to differentiate into lymphatic cells – possibly the first time such cells had been grown in a laboratory.

"We started out by imaging zebrafish, and ended up finding a factor that makes it possible to create lymphatic cells," said senior author Dr. Karina Yaniv, assistant professor of biological regulation at the Weizmann Institute of Science. "That is the beauty of research in developmental biology: The embryo holds the answers, and all we have to do is watch and learn."

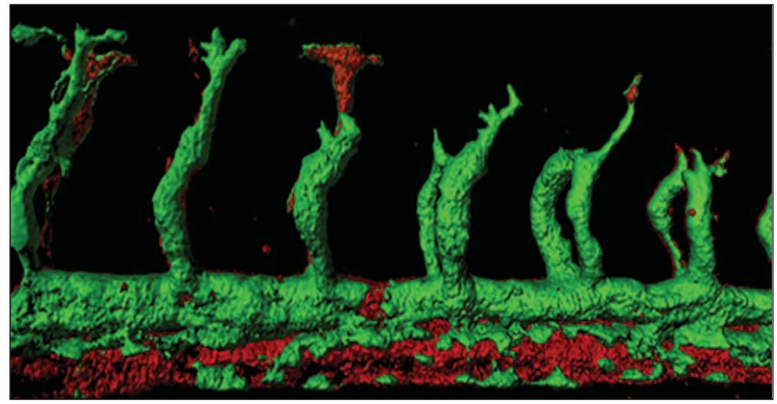


Image: Zebrafish embryos with fluorescent blood vessels helped solve the mystery regarding the origin of the lymphatic system (Photo courtesy of the Weizmann Institute of Science).

New Multimode Microplate Reader Primed to Enhance Biotech Research

A new high-performance, high-speed microplate reader is now available for biotech and other life science laboratories.

The BioTek (Winooski, VT, USA; www.biotek.com) Synergy Neo2 Multi-Mode Reader was designed for speed and ultra-high quality performance. It incorporates BioTek's patented Hybrid technology, which combines independent monochromator-based and filter-based optics in the same instrument. Thus, continuously variable bandwidth quadruple monochromators, sensitive high transmission filter-based optics, and up to four photomultiplier tubes provide ultra-fast measurements with high quality results.

Complementing its sophisticated optic systems, the Synergy Neo2 boasts advanced environment controls, including CO2/O2 control and incubation up to 65 degrees Celsius. Variable shaking supports live cell assays, while cell-based detection is optimized with direct bottom illumination.

The instrument package is powered by BioTek's Gen5 Data Analysis Software and has been configured to integrate seamlessly with the optional BioStackNeo plate stacker, which was designed specifically for use with the Synergy Neo2.

Gary Barush, director of marketing and sales at BioTek, said, "For years BioTek has led the evolution of multimode detection. We are proud to introduce this top-of-the-line reader, which combines best in class performance in all modes with the speed that customers demand. In addition to being optimized for biochemical assay performance, Synergy Neo2 provides unsurpassed results for cell based assay detection, while its modular configuration makes this new level of performance accessible for many budgets."

PRODUCT NEWS

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GENOTYPING ARRAY
Affymetrix

The Axiom Transplant Genotyping Array for research studies is designed to improve transplantation success and individualize donor/patient selection and treatment. The HLA Analysis software enables affordable, high-throughput, accurate analysis of 11 classical loci at 4-digit resolution.

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ISH ASSAY
Advanced Cell Diagnostics

The RNAscope 2.5 enables rapid, accurate assessment of tissue-based biomarker expression across the full spectrum of clinical FFPE tissue samples. The results offer enhanced levels of consistency and reproducibility without the need for lengthy rounds of assay optimization.

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HORIZONTAL CLEAN BENCHES
AirClean Systems

The horizontal clean benches combine Class 100 (ISO 5) process protection with rugged, easy-to-clean polypropylene construction and microprocessor-based controls. These workstations are easy to clean, available in several sizes, and can be placed on a bench top or a cart/stand.

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Mouse Model Shows Role of Interleukin-6 in Spread of Prostate Cancer

Cancer researchers used a recently developed mouse model of metastatic prostate cancer to determine what factors are involved in the processes that trigger cell proliferation and drive progression of the disease.

Investigators at Cold Spring Harbor Laboratory (NY, USA; www.cshl.edu) worked with the RapidCaP GEM (genetically engineered mouse) modeling system that uses surgical injection for viral gene delivery to the prostate.

Discussing their results in the March 31, 2015, online edition of the journal *Cancer Discovery*, the investigators explained that this metastasis was driven by MYC, and not AKT, activation. MYC (v-myc myelocytomatosis viral oncogene homolog protein) is a transcription factor that activates expression of a great number of genes through binding on consensus sequences and recruiting histone acetyltransferases (HATs). By acting as a transcriptional repressor in normal cells, MYC has a direct role in the control of DNA replication. Akt, also known as protein kinase B, is a serine/threonine-specific protein kinase that plays a key role in multiple cellular processes such as glucose metabolism, apoptosis, cell proliferation, transcription, and cell migration.

The investigators showed that cell-cell communication by interleukin-6 (IL-6) drove the AKT-MYC switch through activation of the AKT-suppressing phosphatase PHLPP2 (PH domain and leucine rich repeat protein phosphatase-like), when PTEN and p53 were lost together, but not separately. IL-6 then communicated a downstream program of STAT3 (signal transducer and activator of transcription 3)-mediated MYC activation, which drove cell proliferation.

Loss-of-function mutations of the PTEN (phosphatase and tensin homolog) gene are present in 60% to 70% of metastatic cancers in humans. PTEN acts as a tumor suppressor gene thanks to the role of its protein product in regulation of the cycle of cell division, preventing cells from growing and dividing too rapidly. Mutations in the P53 gene contribute to about half of the cases of human cancer. In these mutants normal p53 protein function is blocked, and the protein is unable to stop multiplication of the damaged cell.

IL-6 is secreted by T-cells and macrophages to stimulate immune response during infection and after trauma, especially burns or other tissue damage leading to inflammation. Advanced/metastatic cancer patients have higher levels of IL-6 in their blood. One example of this is pancreatic cancer, with noted elevation of IL-6 present in patients correlating with poor survival rates. Hence, there is an interest in developing anti-IL-6 agents as therapy against many of these diseases.

"Our research suggests that IL-6 could be a marker for when the disease switches to a more dangerous state that is ultimately hormone therapy-resistant," said senior author Dr. Lloyd Trotman, an associate professor at Cold Spring Harbor Laboratory. "We are really hopeful that translating the IL-6 discovery into the clinics could help us stratify patients into good responders and bad responders. For any hospital this would be a major breakthrough. The gain could be immense; because today's problem is that the variability in response of humans to hormone therapy is amazing. For one man this therapy might be great, might reduce disease burden dramatically for many, many, years, and be an extreme benefit. For others there is almost no response, and it is still not clear to clinicians who is who."

Sorting and Selecting Cancer Cells by Their Motility Will Advance Understanding of Metastatic Processes

In order to develop a better understanding of the mechanisms that cause some cancer cells to break away from the primary tumor and migrate to other parts of the body, a team of cancer researchers has created an instrument for sorting and selecting cancer cells based on their motility.

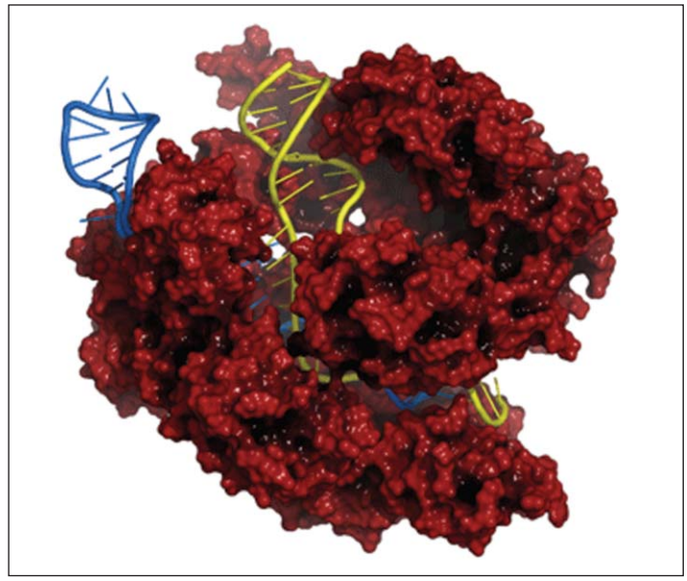
Tumor cell migration toward and into capillaries is an early and key event in cancer metastasis, yet not all cancer cells are imbued with the same capability to do so. This heterogeneity within a tumor is a fundamental property of cancer.

Conventional in vitro migration platforms have so far related to cell populations as an aggregate, which has led to a masking of intrinsic differences among cells. While some migration assays have reported the ability to resolve single cells, these platforms did not provide for selective retrieval of the distinct migrating and non-migrating cell populations for further analysis. Therefore, to study the intrinsic differences in cells responsible for chemotactic heterogeneity, investigators at the University of Michigan (Ann Arbor, USA; www.umich.edu) developed a single-cell migration platform so that individual cells' migration behavior could be studied and the heterogeneous population sorted based upon chemotactic phenotype. Furthermore, after migration, highly chemotactic and non-chemotactic cells were retrieved and proved viable for later molecular analysis of their differences.

In addition, as described in a paper published in the May 18, 2015, online edition of the journal *Scientific Reports*, the investigators modified the migration channel to resemble lymphatic capillaries to better understand how certain cancer cells are able to move through geometrically confining spaces.

"This work demonstrates an elegant approach to the study of cancer cell metastasis by combining expertise in engineering and biology," said senior author Dr. Euisik Yoon, professor of electrical engineering, computer science, and biomedical engineering at the University of Michigan. "In past decades, engineers have developed biological tools with better resolution, higher sensitivity, selectivity, and higher throughput. However, without compelling applications, these engineering tools have little practical relevance. The goal of our lab is to develop tools that can be widely disseminated to the biology community to eventually impact clinical care for patients."

Modifications Should Increase Usefulness of CRISPR-Cas9 Gene Editing



A recent paper described a procedure to modify the CRISPR-Cas9 class of DNA editing nucleases to give them a wider range of usefulness and simultaneously reduce the number of off-target mutations that could be generated.

CRISPRs (clustered regularly interspaced short palindromic repeats) are segments of prokaryotic DNA containing short repetitions of base sequences. Each repetition is followed by short segments of "spacer DNA" from previous exposures to a bacterial virus or plasmid. CRISPRs are found in approximately 40% of sequenced bacteria genomes and 90% of sequenced archaea. CRISPRs are often associated with cas genes that code for proteins related to CRISPRs. The CRISPR/Cas complex comprises a prokaryotic immune system that confers resistance to foreign genetic elements such as plasmids and phages and provides a form of acquired immunity.

Since 2013, the CRISPR/Cas system has been used in research for gene editing (adding, disrupting, or changing the sequence of specific genes) and gene regulation. By delivering the Cas9 protein and appropriate guide RNAs into a cell, the organism's genome can be cut at any desired location. However, the range of sequences that Cas9 can recognize is constrained by the need for a specific protospacer adjacent motif (PAM). As a result, it can often be difficult to target double-stranded breaks (DSBs) with the precision that is necessary for various genome-editing applications.

Investigators at the Harvard Medical School (Boston, MA, USA; www.harvard.edu) reported in the June 22, 2015, online edition of the journal *Nature* that they had developed a technique to modified the commonly used *Streptococcus pyogenes* Cas9 (SpCas9) so it can recognize alternative PAM sequences using structural information, bacterial selection-based directed evolution, and combinatorial design. These altered PAM specificity variants enabled robust editing of endogenous gene sites in zebrafish and human cells not currently targetable by wild-type SpCas9, and their genome-wide specificities were comparable to wild-type SpCas9.

The investigators also found that two smaller-size Cas9 orthologues, *Streptococcus thermophilus* Cas9 (St1Cas9) and *Staphylococcus aureus* Cas9 (SaCas9), functioned efficiently in the bacterial selection systems and in human cells, suggesting that the novel engineering strategies could be extended to Cas9s from other species.

"This work just scratches the surface of the range of PAMs that can be targeted by Cas9," said senior author Dr. J. Keith Joung, professor of pathology at Harvard Medical School. "We believe that other useful properties of the enzyme may be modified by a similar approach, allowing potential customization of many important features."

"This additional evolved variant with increased specificity should be immediately useful to all researchers who currently use wild-type SpCas9 and should reduce the frequencies of unwanted off-target mutations," said Dr. Joung. "Perhaps more important, our findings provide the first demonstration that the activities of SpCas9 can be altered by directed protein evolution."

Image: The CRISPR-Cas9 gene-editing complex from Streptococcus pyogenes (Photo courtesy of Harvard Medical School).

Electron Microscopy Reveals How Viral DNA Survives Extremes of Heat and Acidity

A team of molecular biologists has used advanced electron microscopy techniques to unlock the structure of a unique virus that infects bacteria that live under conditions of extreme heat and acidity.

The nonenveloped, rod-shaped virus SIRV2 (*Sulfolobus islandicus rod-shaped virus 2*) infects the hyperthermophilic acidophile *Sulfolobus islandicus*, a species of archaea that lives in hot springs at 80 degrees Celsius and pH 3. Investigators at the University of Virginia (Charlottesville, USA; www.virginia.edu) wanted to know how the virus managed to safeguard its critical DNA core and whether the virus could be exploited for use as a delivery system for gene therapy in humans.

To study the structure of the viral DNA, the investigators turned to the FEI (Hillsboro, OR, USA; www.fei.com) Titan Krios electron microscope, which had recently become operational at the University of Virginia. The Titan Krios transmission electron microscope (TEM) was tailored for use in protein and cellular imaging. Its revolutionary cryo-based technology and stability was designed to permit a full range of semi-automated applications, including: electron crystallography, single particle analysis, cryo-electron microscopy, and dual-axis cellular tomography of frozen hydrated cell organelles and cells.

The investigators reported in the May 22, 2015, issue of the journal *Science* that they used the Titan Krios to generate a three-dimensional reconstruction of the SIRV2 virion at approximately 0.4 nm resolution. Their study revealed a previously unknown form of virion organization. Although almost half of the capsid protein was unstructured in solution, this unstructured region folded in the virion into a single extended alpha helix that wrapped around the DNA. The DNA was entirely in the A-form, which suggested that there might be a mechanism shared by the virus with bacterial spores for protecting DNA in the most adverse environments.

"Many people have felt that this A-form of DNA is only found in the laboratory under very non-biological conditions, when DNA is dehydrated or dry," said senior author Dr. Edward H. Egelman, professor of biochemistry and molecular genetics at the University of Virginia. "Instead, it appears to be a general mechanism in biology for protecting DNA."

"What is interesting and unusual is being able to see how proteins and DNA can be put together in a way that is absolutely stable under the harshest conditions imaginable," said Dr. Engelman. "We have discovered what appears to be a basic mechanism of resistance – to heat, to desiccation, to ultraviolet radiation. And knowing that, then, we can go in many different directions, including developing ways to package DNA for gene therapy."

Image: The Titan Krios cryo-electron microscope was tailored for use in protein and cellular imaging applications (Photo courtesy of FEI).

Bacterial Toxin Shows Promise as Potential Anticancer Drug

A toxin that increases the virulence of the bacteria that produce it shows promise as a potential anticancer agent.

The bacterium *Vibrio vulnificus* produces and secretes a toxin of the MARTX (multifunctional-autoprocessing repeats-in-toxin) family. MARTX toxins serve as delivery platforms for cytotoxic effector domains. One of these effector domains, called the domain of unknown function in position 5 (DUF5), has been shown to increase the potency of the *V. vulnificus* MARTX toxin in mouse virulence studies, indicating DUF5 directly contributes to pathogenesis. DUF5 is localized in the plasma membrane dependent upon its C1 domain, and the cells become rounded dependent upon its C2 domain.

In the current study, investigators at Northwestern University (Chicago, IL, USA; www.northwestern.edu) used a combination of genetic, cell biological, and biochemical strategies to probe the mechanism of action of the MARTX C2 domain, to understand the connection of DUF5 to both cytotoxicity and increased virulence of the pathogen.

They reported in the June 8, 2015, online edition of the journal *Nature Communications* that DUF5 was a site-specific endopeptidase that cleaved both Ras and the closely related small GTPase Rap1. Both proteins are critical for activation of the innate immune response during infection, which explains the crucial role of this effector domain in the increased virulence of *V. vulnificus* strains that have DUF5.

In addition, the investigators showed that the *V. vulnificus* MARTX protein could inhibit cancer cell growth by deactivating Ras. This linkage seems justified, as Ras signaling stimulates cell growth and division, and overactive Ras signaling can ultimately lead to cancer. Ras is the most common oncogene in human cancer – mutations that permanently activate Ras are found in 20%–25% of all human tumors and up to 90% in certain types of cancer such as pancreatic cancer.

"What is unique about this study is the ability of the toxin to cleave Ras, rather than modify it, which is a novel mechanism for inactivating Ras," said senior author Dr. Karla Satchell, professor of microbiology and immunology at Northwestern University. "Ras is important for cell proliferation in cancer, so the toxin could potentially be developed as a treatment for different types of tumors. It has been known that Ras has a role in cancer development, and targeting Ras has been one of the hardest challenges of cancer research and drug discovery."

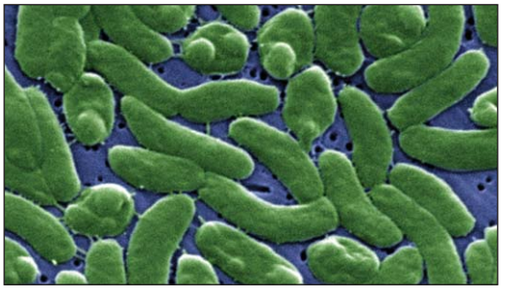


Image: A false-color scanning electron micrograph (SEM) of Vibrio vulnificus bacteria (Photo courtesy of the CDC).

New Version of Old Drug Shows Promise for Treating Drug-Resistant Tuberculosis

A team of molecular microbiologists has determined the mechanism by which the *Streptomyces*-derived antibiotic griselimycin blocks the growth of *Mycobacterium tuberculosis*, the bacterium responsible for causing more than eight million cases of tuberculosis annually on a worldwide basis.

Investigators from the Helmholtz Center for Infection Research (Braunschweig, Germany; www.helmholtz-hzi.de), other German research institutes, and the biomedical company Sanofi (Paris, France; www.sanofi.com) were interested in exploring the possibility of using griselimycin or one of its derivatives for treating drug resistant tuberculosis; while this drug had been evaluated in the 1960's it had suffered in comparison to others. However, *M. tuberculosis* has developed resistance to most of those other drugs, and development of replacements is a top priority.

The investigators reported in the June 5, 2015, issue of the journal *Science* that a variant of griselimycinm, cyclohexylgriselimycin, was particularly effective against *M. tuberculosis*, in cells and when administered orally to an animal model.

The effectiveness of cyclohexylgriselimycin was found to be due to the drug's inhibition of the *M. tuberculosis* DNA polymerase sliding clamp DnaN. A DNA clamp, also known as a sliding clamp, is a protein fold that serves as a processivity-promoting factor in DNA replication. Processivity is an enzyme's ability to catalyze consecutive reactions without releasing its substrate. As a critical component of the DNA polymerase III holoenzyme, the clamp protein binds DNA polymerase and prevents this enzyme from dissociating from the template DNA strand. The clamp-polymerase protein–protein interactions are stronger and more specific than the direct interactions between the polymerase and the template DNA strand; because one of the rate-limiting steps in the DNA synthesis reaction is the association of the polymerase with the DNA template, the presence of the sliding clamp dramatically increases the number of nucleotides that the polymerase can add to the growing strand per association event. The presence of the DNA clamp can increase the rate of DNA synthesis up to 1,000-fold compared with a nonprocessive polymerase.

As inhibiting the DNA clamp is a completely different mechanisms from those of antibiotics now used against tuberculosis and other bacterial pathogens, the investigators consider that the risk of developing resistance to cyclohexylgriselimycin is low.

"We hope that cyclohexylgriselimycin will become an agent that can even be used against resistant tuberculosis pathogens in the future and contributes to a more successful fight against this dreadful disease," said senior author Dr. Rolf Müller, head of the department of microbial natural products at the Helmholtz Centre for Infection Research. "In the tuberculosis pathogen, the substance binds to the so-called DNA clamp and thus suppresses the activity of the DNA polymerase enzyme, which multiplies the genetic information inside the cell. We resumed the work on this agent and optimized it such that it shows excellent activity in the infection model – even against multi-resistant tuberculosis pathogens."

A Drug That Prevents Lung Damage Protects Mice with Influenza Infection

A novel approach for treating infection by the influenza virus focuses on strengthening the small blood vessels in the lung of the victim so they do not leak fluids, which can lead to respiratory failure.

Seasonal influenza virus infections cause hundreds of thousands of deaths annually while viral mutation raises the threat of the emergence of a novel pandemic strain. Severe influenza virus infections are complicated by respiratory failure due to the development of microvascular leaks that lead to acute lung injury. Antiviral drugs exhibit limited efficacy unless administered early and may induce viral resistance. For these reasons targeting the host response directly has been proposed as a novel therapeutic strategy with the added potential benefit of not eliciting viral resistance.

To test the potential therapeutic benefits of enhancing lung endothelial barrier integrity, investigators at St. Michael's Hospital (Toronto, Canada; www.stmichaelshospital.com) treated influenza infected mice with the drug Vasculotide. This drug is a synthetic peptide-based growth factor that targets Tie-2, a receptor on specialized cells of the hematopoietic and vascular systems. Tie-1 and Tie-2 comprise the cell-surface receptors that bind and are activated by the angiopoietins, (Ang1, Ang2, Ang3, and Ang4). The angiopoietins are protein growth factors required for the formation of blood vessels.

Results published in the June 5, 2015, online edition of the journal *Scientific Reports*, revealed that Vasculotide improved survival in mouse models of severe influenza, even if administered as late as 72 hours after infection. In one study 100% of infected mice died within one week, while more than 80% of a similar group treated with Vasculotide survived.

The benefits of the drug were observed using three strains of the virus and two strains of mice. The effect required Tie2, was independent of viral replication, and did not impair lung neutrophil recruitment.

Senior author Dr. Warren Lee, a cell biologist at St. Michael's Hospital, said, "While this research was conducted in mice, the results were exciting, since the drug was effective in two different strains of mice and three different strains of flu. Since the mechanism of blood vessels leaking into lungs is common throughout animals, I am optimistic the drug could be effective in animals other than mice, including humans."

3D Scanning and Printing Technology Enable Complex Nerve Regeneration in Rat Model

A novel three-dimensional printing approach has enabled the regeneration of a complex nerve in a rat model system.

Investigators at the University of Minnesota (Minneapolis, USA; www.umn.edu) and their colleagues at several other research institutes used sophisticated imaging technology to produce a three-dimensional map of the structure of a rat's sciatic nerve. A custom-built three-dimensional printer was then used to fabricate a silicone guide for regrowth of the nerve. The guide incorporated both physical and biochemical cues to promote regeneration of the nerve.

In vitro studies showed that three-dimensional printed physical and biochemical cues in the guide provided axonal guidance and chemotractant/chemokinetic functionality.

The guide was implanted into a rat by surgically grafting it to the cut ends of the sciatic nerve. Results published in the September 18, 2015, online edition of the journal *Advanced Functional Materials* revealed that in vivo studies examining the regeneration of bifurcated injuries across a 10 millimeter complex nerve gap in rats showed that the three-dimensional printed scaffolds achieved successful regeneration of complex nerve injuries, resulting in enhanced functional return of the regenerated nerve.

"This represents an important proof of concept of the three-dimensional printing of custom nerve guides for the regeneration of complex nerve injuries," said senior author Dr. Michael McAlpine, professor of mechanical engineering at the University of Minnesota. "Someday we hope that we could have a three-dimensional scanner and printer right at the hospital to create custom nerve guides right on site to restore nerve function. The exciting next step would be to implant these guides in humans rather than rats. In cases where a nerve is unavailable for scanning, there could someday be a "library" of scanned nerves from other people or cadavers that hospitals could use to create closely matched three-dimensional-printed guides for patients."

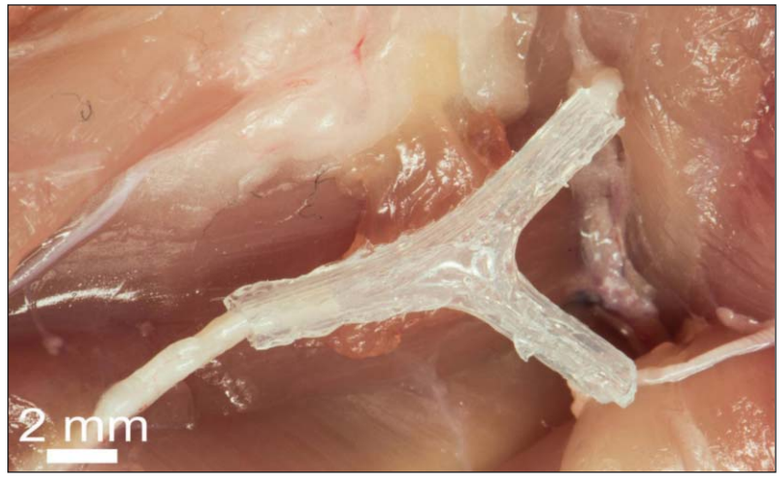


Image: A three-dimensional (3D) printed nerve regeneration pathway implanted in a rat (Photo courtesy of the University of Minnesota College of Science and Engineering).

Entamoeba Hystolytica Manipulates Host Ion Transport Proteins to Cause Cell Death

A team of molecular microbiologists has found that immunity to infection by the parasitic amoeba *Entamoeba hystolytica* could be induced in humans by using RNAi (interfering RNA) technology to block the genes controlling the activity of potassium ion transporter proteins.

Investigators at the University of Virginia (Charlottesville, USA; www.virginia.edu) borrowed techniques usually used by cancer researchers to search for human genes that respond to interaction with *E. histolytica*. They reported in the September 8, 2015, online edition of the journal *Scientific Reports* that they had used RNAi technology to create a library of bladder cancer cells with a multitude of independent, silenced genes. Populations of these cells were exposed to the parasite, and surviving cells were re-cultured and then exposed to the parasite again. After nine generations, cells were showing resistance to destruction by *E. histolytica*.

The genes of these resistant cells were analyzed with next-generation sequencing technology, which identified 281 candidate susceptibility genes. Bioinformatics analyses revealed that ion transporters were significantly enriched among these susceptibility genes, and that potassium (K+) channels were the most common transporter identified. Their importance was further supported by colon biopsy of humans with amebiasis that demonstrated suppressed K+ channel expression.

Inhibition of human K+ channels by genetic silencing, pharmacologic inhibitors, and with excess K+ protected diverse cell types from *E. histolytica*-induced death. Thus, it was apparent that contact with *E. histolytica* parasites triggered K+ channel activation and K+ efflux by intestinal epithelial cells, which preceded cell killing. Specific inhibition of Ca2+-dependent K+ channels was highly effective in preventing amebic cytotoxicity in intestinal epithelial cells and macrophages.

"There is a clear need for new drugs targeting *E. histolytica*," said senior author Dr. William A. Petri Jr., professor of internal medicine and pathology at the University of Virginia. "Right now there is a single antibiotic that works against this parasite. We know that eventually the parasite will develop resistance to the antibiotic and at that point there is no plan B. This could be the plan B – targeting the human genes that enable the parasite to cause disease."

PRODUCT NEWS

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FUME HOOD
Air Science

The PURAIR 5 hoods feature a high level of operator protection where routine work is being carried out. The ductless design eliminates installation costs and allows the unit to be positioned over a sink or bench top apparatus. Three models are available with a choice of 24", 36" or 48" widths.

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SPIRAL MEMBRANES
Alfa Laval

The PP spiral membranes are compact with a larger filtration area for better performance and the possibility to produce a wider product range. The membranes offer benefits like reduction of water/chemical use, as well as longer service life, meaning less maintenance and less downtime.

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HIGH-THROUGHPUT READER
Berthold Technologies

The bScreen combines the performance of µArray formats with the information available from label-free technologies. With a footprint of only 66 x 61 cm2, it substitutes a fluorescence µArray reader and a conventional label-free system (e.g. SPR) in a single instrument.

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Popular Microscope Gets LED Illumination Feature

A popular microscope used for both clinical and research applications is now available with LED illumination.

The Leica (Wetzlar, Germany; www.leica-microsystems.com) DM2500 and DM2500 LED microscopes represent a class of tools for demanding tasks in life science routine and research applications. With their powerful transmitted light illumination, high-quality optical performance, and state-of-the-art accessories, the Leica DM2500 and DM2500 LED are especially well suited for challenging life science research tasks that require differential interference contrast or high-performance fluorescence.

The difference between the two microscopes is their illumination: The Leica DM2500 LED is equipped with LED illumination for transmitted light, whereas the Leica DM2500 works with halogen. Both types of illumination render a realistic impression of the colors of the sample, so that users in clinical applications, such as the frequently used HE specimen staining, are able to assess the colors of their samples accurately. With the launch of the Leica DM2500 LED, Leica Microsystems has completed its Leica DM1000 to 3000 series of microscopes. All the models in this series are now available with LED illumination. The microscopes are certified for in vitro diagnostics (IVD) use.

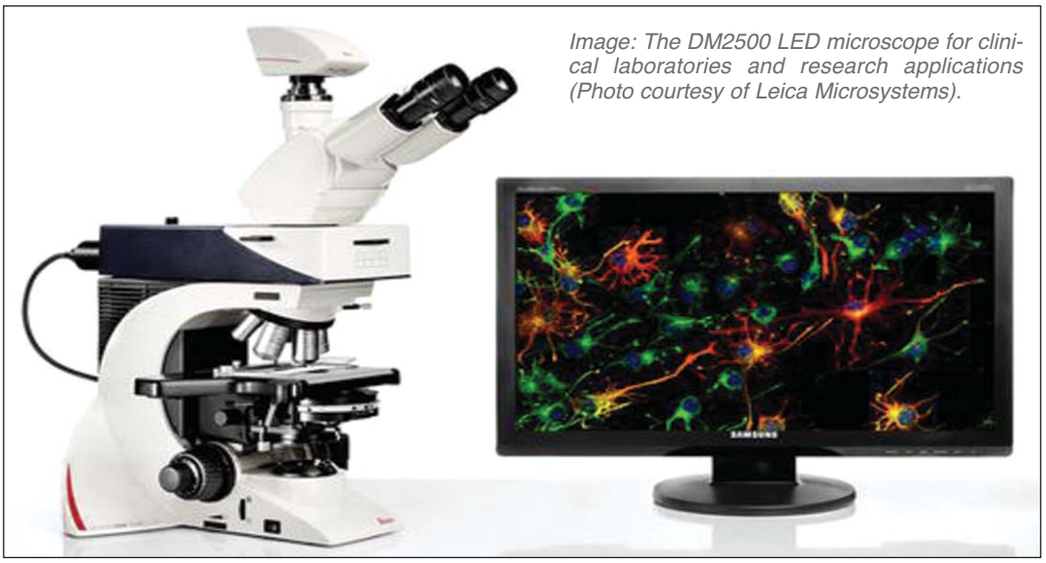


Image: The DM2500 LED microscope for clinical laboratories and research applications (Photo courtesy of Leica Microsystems).

The ultra-bright LED illumination of the newly released Leica DM2500 LED offers a constant color temperature at all light intensities, enabling particularly fine differentiation of colors in stained specimens. Users benefit from the brightness and color accuracy of the LED illumination in all other transmitted light contrasting techniques, such as brightfield, polarized light, and darkfield.

"The specially-developed LED illumination makes the Leica DM2500 LED an ideal microscope for challenging experiments requiring different contrasting techniques and for users who prefer a manual instrument," said Dr. Jasna Gilbert, product manager at Leica Microsystems. "The Leica DM2500 LED has now completed our DM1000 to 3000 series. All the models are available with either LED or halogen illumination. Besides the new illumination, the Leica DM2500 LED offers all the other benefits of the microscope series such as the unique ergonomics design for user comfort and convenience."

Cancer Immunotherapy Method Relies On Artificial Magnetic Antigen Presenting Cells

Cancer researchers have developed a method based on magnetic nanoparticles that enables the rapid extraction, enrichment, and expansion of a T-cell population that shows great promise as a tool for immunotherapy.

Adoptive immunotherapy can induce long-term tumor regression, but widespread adoption of this approach has been limited by the cost and complexity of generating tumor-specific T-cells.

Investigators at Johns Hopkins University (Baltimore, MD, USA; www.jhu.edu) developed an improved method for generating tumor-specific T-cells to use for adoptive immunotherapy. Their method employed paramagnetic, nanoscale artificial antigen presenting cells (aAPC) to rapidly expand tumor-specific T-cells from rare naive precursors.

Thus far, aAPCs have been synthesized by coupling T-cell activating proteins such as CD3 or MHC-peptide to micron-sized beads. Nanoscale platforms have different trafficking and biophysical interaction properties and may allow development of new immunotherapeutic strategies. Thus, for the current study, the investigators manufactured aAPCs from biocompatible iron-dextran paramagnetic particles (50–100 nanometers in diameter).

Senior author Dr. Jonathan Schneck, professor of pathology, medicine, and oncology at Johns Hopkins University, said, "The challenge has been to train these cells efficiently enough, and get them to divide fast enough, that we could use them as the basis of a therapy for cancer patients. We have taken a big step toward solving that problem."

Bacteria-Based Biosensor Detects Zinc Deficiency

A series of genetic engineering steps led to the development of a bacterial biosensor capable of visually distinguishing levels of zinc, a critical micronutrient.

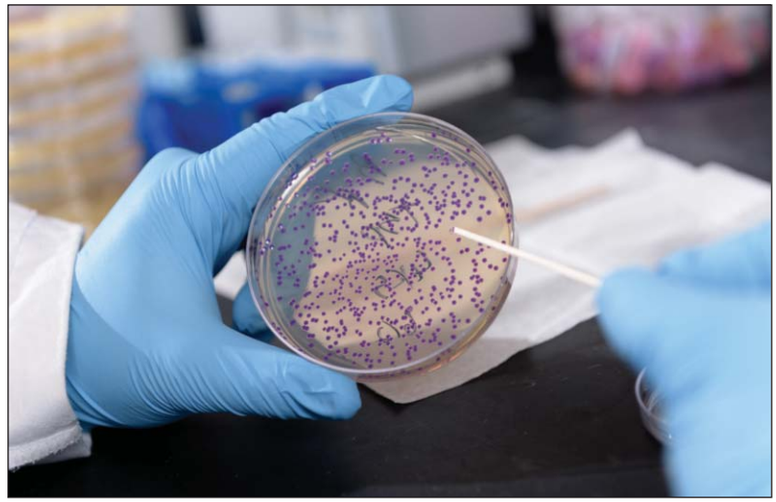
Micronutrient deficiencies, including zinc deficiency, are responsible for hundreds of thousands of deaths annually. A key obstacle to allocating scarce treatment resources is the ability to measure population blood micronutrient status inexpensively and quickly enough to identify those who most need treatment.

To overcome this obstacle a team of molecular microbiologists at the Georgia Institute of Technology (Atlanta, USA; www.gatech.edu) developed a novel approach for inexpensive screening of micronutrients, with zinc being the test case.

Towards this end, the investigators genetically engineered a strain of *Escherichia coli* to produce different colored pigments (violacein, lycopene, and beta-carotene) in response to different extracellular zinc levels. Genes for the pigments were taken from other organisms and inserted into the *E. coli* on a plasmid. The red and orange colors, lycopene and beta-carotene, were produced by genes taken from *Pantoea anantis*, a plant pathogen. The purple color, violacein, came from a soil bacterium.

Obtaining discrete color states in the carotenoid pathway required precise engineering of the *E. coli's* metabolism to prevent a reaction at low zinc concentrations but allow complete reaction at higher concentrations, and all under the constraints of the bacterium's natural regulator limitations. A combination of gene dosage, post-transcriptional, and post-translational regulation was necessary to allow visible color change over physiologically relevant ranges representing a small fraction of the regulator's dynamic response range, with further tuning possible by modulation of precursor availability.

In practice, a pellet of the engineered bacteria was mixed with the plasma from a human subject. The *E. coli* multiplied, producing the color corresponding to the level of zinc in the sample. Purple corresponded to dangerously low levels, while red indicated borderline levels, and orange normal levels. The color was readily visible without any diagnostic or other electronic equipment.



"We think this is just enough technology to meet the needs," said Dr. Mark Styczynski, assistant professor of chemical and bio-molecular engineering at the Georgia Institute of Technology. "Information we can provide could one day help nutritional epidemiologists and non-governmental organizations determine the populations of people that may need interventions to address nutritional deficiencies."

"The general idea of bio-sensing is certainly out there, but we have taken the step of developing a system that does not require equipment in the field," said Dr. Styczynski. "We believe this will work well in low-resource areas. This is a convincing proof-of-principle, and we hope to begin the translational aspects of this system based on what we have already shown. It is a matter now of reducing this to practice for something that will ultimately be useful."

The novel assay for zinc deficiency was described in a paper published in the September 2015 issue of the journal *Metabolic Engineering*.

Image: A plate containing E. coli producing a purple pigment indicative of low levels of zinc. The bacterium could be used to detect nutritional deficiencies in resource-limited areas of the world (Photo courtesy of Rob Felt, Georgia Institute of Technology).

Mouse Model Shows Potential of Personalized Cancer Treatment Based on Live Cell Vaccination

A novel personalized approach to cancer immunotherapy is based on sponge-like "cryogels" that are loaded with a sampling of the patient's tumor cells together with immune system-stimulating reagents and then injected under the skin.

Cryogels are a type of hydrogel made up of cross-linked hydrophilic polymer chains that can hold up to 99% water. They are created by freezing a solution of the polymer during the gelling process. When thawed to room temperature, the substance turns into a highly interconnected pore-containing hydrogel, which is similar in composition to bodily soft tissues in terms of their water content, structure, and mechanics.

Investigators at Harvard University (Cambridge, MA, USA; www.harvard.edu) worked with a mouse melanoma model. They injected some of these animals with sponge-like macroporous cryogels that had been loaded with GM-CSF (granulocyte macrophage colony-stimulating factor), serving as a DC (dendritic cell) enhancement factor. GM-CSF is a cytokine that functions as a white blood cell growth factor. GM-CSF stimulates stem cells to produce granulocytes (neutrophils, eosinophils, and basophils) and monocytes. Monocytes exit the circulation and migrate into tissue, whereupon they mature into macrophages and dendritic cells. Thus, it is part of the immune/inflammatory cascade, by which activation of a small number of macrophages can rapidly lead to an increase in their numbers, a process crucial for fighting infection.

In addition to GM-CSF, the cryogels were loaded with CpG ODN (CpG oligodeoxynucleotide, a molecule with immunostimulatory properties) that served as a DC activating factor and with a number of cancer cells harvested from the same mouse. These cryogels were injected subcutaneously into the mice to localize transplanted tumor cells and deliver immunomodulatory factors in a controlled spatiotemporal manner.

Results published in the August 12, 2015, online edition of the journal *Nature Communications* revealed that these vaccines elicited local infiltrates composed of conventional and plasmacytoid DCs, with the subsequent induction of potent, durable, and specific anti-tumor T-cell responses in the melanoma model. These responses induced tumors to shrink and even provided prophylactic protection from tumor growth. Cryogels could be delivered in a minimally invasive manner, bypassed the need for genetic modification of transplanted cancer cells and provided sustained release of immunomodulators.

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AUTO INJECTOR
Bespak

The Syrina 2.25 is the latest addition to the Syrina product range of self-injection devices for drug delivery. The line spans from assisted syringes with needle safety features through to fully functioning auto-injectors. All products in the range utilize Bespak's VapourSoft powerpack system.

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TEST COLUMNS
Biotage

The ISOLUTE PLD+ 96-well plates and columns combine protein and phospholipid removal into a single product providing effective and simple sample clean up for LC-MS/MS analysis. The format is ideal for lower throughput applications or for labs that have variable sample numbers to process.

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MAGNETIC STIRRER
Capp

The CappRondo is a compact device that works at a maximum speed of 1500rpm. It is manufactured with a stainless steel top surface to resist moderate contamination of harsh chemicals. The adjustable speed and timer function can be set and monitored on a modern real-time digital display.

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Researchers Develop Novel Transcutaneous Influenza Vaccination Based on Dissolving Microneedle Patch

Vaccination via a biodegradable microneedle patch was shown to generate immune response to various strains of the influenza virus that were equal to or stronger than those induced by traditional hypodermic needle injection.

Previous attempts using microneedles made of silicon or metal were not successful primarily due to the risk of the needles breaking off in the skin, leaving tiny fragments behind. To avoid this problem, investigators at Osaka University (Japan; www.osaka-u.ac.jp) prepared microneedle patches from hyaluronic acid, a naturally occurring and water-soluble biological material. The "MicroHyala" microneedle patch was loaded with the material to be injected and then applied like a plaster. The needles pierced the top layer of skin and then dissolved into the body, taking the vaccine with them.

In the current study the investigators examined the clinical safety and efficacy of the MicroHyala vaccination method using MH (flu-MH), which contains trivalent influenza hemagglutinins (15 micrograms each). Subjects were treated transcutaneously (TCI group) with a flu-MH microneedle patch, and were compared with subjects who received subcutaneous injections (SCI group) of a solution containing 15 micrograms of each influenza antigen.

Results published in the July 2015 issue of the journal *Biomaterials* revealed that no severe local or systemic adverse events were detected in either group. Immune responses against A/H1N1 and A/H3N2 strains were induced equally in the TCI and SCI groups. Moreover, the efficacy of the vaccine against the B strain in the TCI group was stronger than that in the SCI group.

"Our novel transcutaneous vaccination using a dissolving microneedle patch is the only application vaccination system that is readily adaptable for widespread practical use," said senior author Dr. Shinsaku Nakagawa, professor of medical pharmacy at Osaka University. "Because the new patch is so easy to use, we believe it will be particularly effective in supporting vaccination in developing countries."

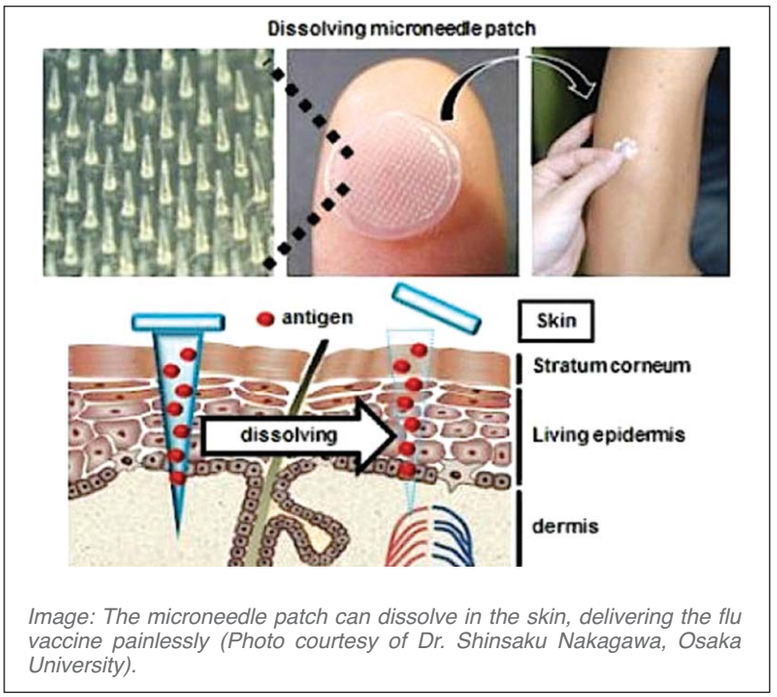

Image: The microneedle patch can dissolve in the skin, delivering the flu vaccine painlessly (Photo courtesy of Dr. Shinsaku Nakagawa, Osaka University).

"We were excited to see that our new microneedle patch is just as effective as the needle-delivered flu vaccines, and in some cases even more effective," said Dr. Nakagawa. "We have shown that the patch is safe and that it works well. Since it is also painless and very easy for non-trained people to use, we think it could bring about a major change in the way we administer vaccines globally."

Glycated Proteins and Oxidized Lipoproteins but Not Insulin Resistance Linked to CVD Risk

Heart disease researchers working with a pig model system identified glycated proteins and oxidized low-density lipoproteins (oxLDL) as biomarkers for cardiovascular disease (CVD) risk but did not find a similar association between CVD risk and insulin resistance.

Investigators at the University of North Carolina (Chapel Hill, USA; www.unc.edu) chose to work with pigs, since pigs, like humans, develop coronary artery and aortic atherosclerosis and insulin resistance. In addition, pigs have been used in many studies to define the mechanisms that mediate increased atherosclerosis in diabetes.

Results published in the July 6, 2015, online edition of the journal *PLoS One* revealed that 20 pigs developed severe and diffuse distal coronary artery while the other 17 pigs had substantially less coronary artery atherosclerosis. All 37 pigs had blood pressure measurements in a range that would be considered hypertensive in humans and developed elevations in total, LDL, and HDL cholesterol, weight gain, increased backfat, and increased insulin resistance without overt diabetes. Five additional pigs fed regular pig chow also developed increased insulin resistance but essentially no change in the other variables and little to no detectible coronary atherosclerosis.

The 20 high fat/high NaCl diet-fed pigs with severe and diffuse distal coronary artery atherosclerosis had substantially greater increases in oxidized LDL and fructosamine consistent with increased protein glycation. Insulin resistance was not associated with atherosclerosis severity.

Gene Expression Kit Designed for High-Throughput Automated Usage

A newly released kit for gene expression measurement was designed for high-throughput use with 384-well microplates. The Affymetrix (Santa Clara, CA, USA; www.affymetrix.com) QuantiGene Singleplex Assay does not require nucleic acid purification, reverse transcription, or PCR amplification. Packaged for use on 384-well microplates, the assay is readily adaptable for automated high-throughput screening.

The manufacturer recommends using the QuantiGene assay for screening of compounds in drug discovery, for biomarker validation, and in siRNA (small, inhibiting RNA) knockdown studies. The assay works with a wide range of sample types, including heavily degraded and cross-linked RNA in FF-PE (formalin fixed paraffin embedded) samples and RNA circulating in blood.

"This new, automation-friendly 384-well assay format fits with current workflows because cells are most commonly cultured in 384-well plates for high-throughput screening," said Brian McLucas, product manager at Affymetrix. "Furthermore, the limiting step with qPCR is RNA purification, which is completely avoided with QuantiGene assays. Gene expression-based high-throughput screening of hundreds of thousands of compounds can be carried out in just weeks."

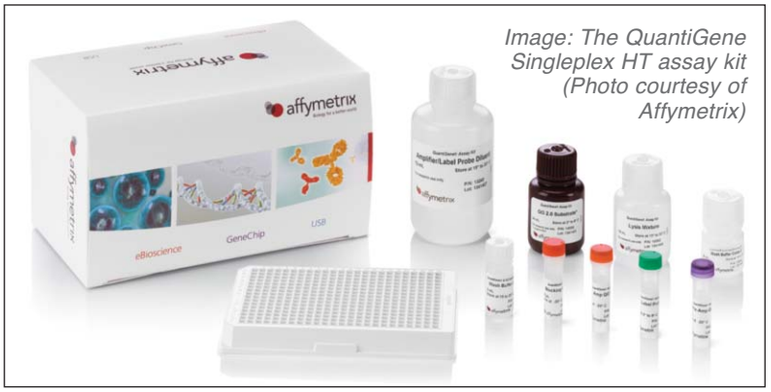

Image: The QuantiGene Singleplex HT assay kit (Photo courtesy of Affymetrix)

Orally-Delivered Curcumin-Loaded Microparticles Effectively Treat Mouse Model from Ulcerative Colitis

Microparticles (MPs) loaded with the efficient anti-inflammatory agent curcumin were found to effectively treat a mouse model of ulcerative colitis.

Ulcerative colitis is a chronic relapsing disease associated with uncontrolled inflammation in the gastrointestinal tract. It is a subtype of inflammatory bowel disease (IBD) and often affects the innermost mucosa of the intestine. The goal for ulcerative colitis therapy is to control inflammation, heal the mucosa, and reduce the need for surgery and hospitalization.

In the current study, investigators at Georgia State University (Atlanta, USA; www.gsu.edu) used an emulsion-solvent evaporation method to fabricate MPs from pH-sensitive Evonik (Essen, Germany; www.evonik.com) Eudragit S100 and poly(lactide-*co*-glycolide) (PLGA). Eudragit S100 is composed of anionic copolymers based on methacrylic acid and methyl methacrylate that forms effective and stable enteric coatings with a fast dissolution in the upper bowel. PLGA is a copolymer used in a variety of [US] Food and Drug Administration approved therapeutic devices, owing to its biodegradability and biocompatibility. The MPs were loaded with curcumin (an efficient anti-inflammatory agent). As of June 2015, there were 116 clinical trials evaluating the possible anti-disease effect of curcumin in humans, as registered with the [US] National Institutes of Health, including studies on cancer, gastrointestinal diseases, cognitive disorders, and psychiatric conditions.

The spherical MPs that were produced had a desirable particle size ranging from 1.52 to 1.91 microns. Their loading efficiency could be regulated by changing the weight ratios of Eudragit S100 and PLGA, with some MPs exhibiting loading efficiencies over 80%. The fast release of curcumin from MPs in buffers (pH 1.2 and 6.8) could be significantly decreased by increasing the PLGA content. Eudragit 100/PLGA MPs with a weight ratio of 1:2 (MPs-4) were able to maintain sustained release of curcumin, releasing approximately 48% of the initial drug load at pH 7.2–7.4 during a 20 hour-incubation.

Results of in vivo experiments published in the August 1, 2015, online edition of the journal *Colloids and Surfaces B: Biointerfaces* revealed that orally administered MPs-4 had a superior therapeutic efficiency in alleviating colitis in an ulcerative colitis mouse model, compared to free curcumin.

"Orally administered microparticles may offer an efficient drug delivery system because they are characterized by a high drug loading capacity and may target colitis tissues based on abnormalities," said senior author Dr. Didier Merlin, professor of biomedical sciences at Georgia State University.

STERILITY TESTING HARDWARE
EMD Millipore

The Steritest Symbio sterility testing pumps are designed for testing in a laminar flow hood, isolator or clean room. Software allows easy creation and management of test methods and simplified synchronization, and operators are given step-by-step assistance throughout the testing procedure.

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MICROSCOPY ILLUMINATOR
Excelitas Technologies

The X-Cite TURBO is designed for microscopy imaging and detection applications. It provides maximum excitation power for all standard color wavelengths, and features mercury-free operation, virtually zero maintenance, and instant on/off capabilities.

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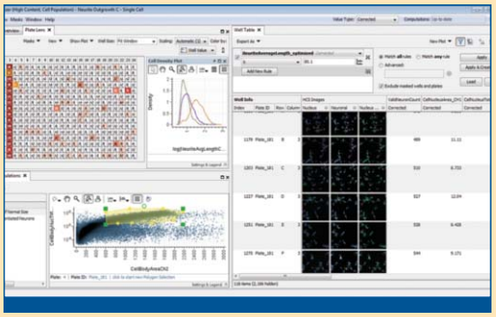
IMAGE SCREENING PLATFORM
Genedata



The Genedata Screener version 13.0 includes context-specific image displays, and automated analysis from single cells to end results. Added benefits include interactive definition and analysis of cell populations, and advanced statistics/visualizations for feature exploration and reduction.

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Peroxidase Mimic Outperforms Natural Horseradish Peroxidase in ELISA Test

A test-of-concept study demonstrated that a synthetic catalyst that mimics the action of horseradish peroxidase (HRP) could increase the sensitivity of a colorimetric enzyme-linked immunosorbent assay (ELISA) for human prostate surface antigen (PSA) by more than 110-fold. Peroxidase mimics with dimensions on the nanoscale have received great interest as emerging artificial enzymes for biomedicine and environmental protection. While a variety of peroxidase mimics have been developed recently, limited progress has been made toward improving their catalytic efficiency.

In a study published in the September 3, 2015, online edition of the journal *ACS Nano*, investigators at Michigan Technological University (Houghton, USA; www.mtu.edu) and colleagues at Louisiana State University (Baton Rouge, USA; www.lsu.edu) and the University of Texas at Dallas (USA; www.utdallas.edu) described a novel peroxidase mimic made by depositing Ir (iridium) atoms as ultrathin skins (a few atomic layers) on Pd (palladium) nanocubes.

These Pd–Ir nanocubes exhibited significantly enhanced efficiency, with catalytic constants more than 20- and 400-fold higher than those of an older version of Pd cubes and horseradish peroxidase (HRP), respectively. In a proof-of-concept demonstration, the Pd–Ir nanocubes were used in a colorimetric ELISA for human prostate surface antigen (PSA). The modified assay was found to have a detection limit of 0.67 picograms per milliliter, which was about 110-fold lower than that of the conventional HRP-based ELISA using the same set of antibodies and the same procedure.

The Pd–Ir nanocubes were prepared by chemists at the Michigan Technological University. Investigators at Louisiana State University conducted theoretical calculations, and colleagues at the University of Texas at Dallas obtained high-resolution electron microscopy images.

"After surgery, it is vital to detect a tiny amount of prostate antigen, because otherwise you can get a false negative and perhaps delay treatment for cancer," said senior author Dr. Xiaohu Xia, assistant professor of chemistry at Michigan Technological University. "We wanted to develop a mimic peroxidase that was substantially more efficient than the natural peroxidase, which would lead to a more-sensitive PSA test. Our ultimate goal is to further refine our system for use in clinical diagnostic laboratories."

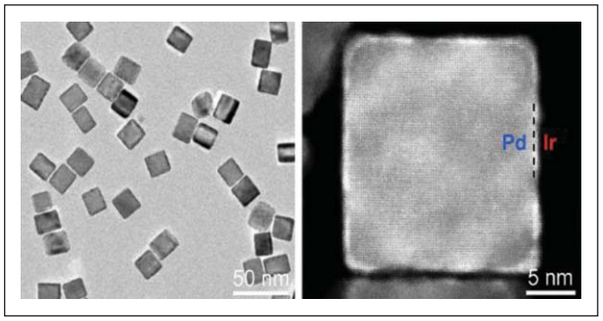

Image: A new catalyst that improved the sensitivity of the standard PSA ELISA test by about 110-fold was made of palladium nanocubes coated with iridium (Photo courtesy of Dr. Xiaohu Xia, Michigan Technological University).

Modifying Macrophage Microenvironment Reduces Tuberculosis Virulence

The virulence of the bacteria causing latent tuberculosis infections can be reduced by modifying the microenvironment inside the macrophages that host the pathogen.

Mycobacterium tuberculosis must sense and adapt to host environmental cues to establish and maintain an infection. The two-component regulatory system PhoPR plays a central role in sensing and responding to acidic pH within the macrophage and is required for *M. tuberculosis* intracellular replication and growth in vivo. Therefore, the isolation of compounds that inhibit PhoPR-dependent adaptation may pave the way for development of new therapies to treat tuberculosis.

Investigators at Michigan State University (East Lansing, USA; www.msu.edu) screened more than 273,000 different compounds while searching for those that could attenuate or eradicate *M. tuberculosis*.

They identified the carbonic anhydrase inhibitor ethoxzolamide as being able to modify PhoPR regulation and reduce virulence of the tuberculosis bacterium. Ethoxzolamide binds and inhibits carbonic anhydrase, which plays an essential role in facilitating the transport of carbon dioxide and protons in the intracellular space, across biological membranes and in the layers of the extracellular space. The primary function of the enzyme in animals is to interconvert carbon dioxide and bicarbonate to maintain acid-base balance in blood and other tissues, and to help transport carbon dioxide out of tissues. The inhibition of this enzyme affects the balance of applicable membrane equilibrium systems. Carbonic anhydrase inhibitors are primarily used for the treatment of glaucoma.

The investigators reported in the August 2015 issue of the journal *Antimicrobial Agents and Chemotherapy* that by employing quantitative single-cell imaging of a PhoPR-dependent fluorescent reporter *M. tuberculosis* strain, they were able to demonstrate that ethoxzolamide inhibited PhoPR-regulated genes in infected macrophages and mouse lungs. Moreover, ethoxzolamide reduced *M. tuberculosis* growth in both macrophages and infected mice.

"The single biggest reason for the evolution of drug-resistant strains is the long course of treatment," said Dr. Abramovitch. "It is difficult for a patient to complete the entire antibiotic course required to kill all of the bacteria. Shortening the duration will help slow the development of these resistant strains. We do not necessarily have to find drugs that kill TB, we just need to find ones that interfere with the bug's ability to sense and resist the immune system. By giving the immune system a helping hand, natural defenses can then kill the bacteria."

Diagnosing Liver Cancer with Genetically Modified Probiotic Bacteria

A genetically engineered variety of the probiotic bacterium *Escherichia coli* Nissle 1917 was used to generate a luminescent diagnostic biomarker that could be detected in the urine of rodents with liver tumors.

Investigators at the Massachusetts Institute of Technology (Cambridge, MA, USA; www.mit.edu) and the University of California, San Diego (USA; www.ucsd.edu) genetically engineered *E. coli* Nissle 1917 to carry the gene that encodes a lacZ reporter enzyme, which would normally cleave lactose into glucose and galactose. For the current study galactose linked-luciferin was provided as the substrate in test rodents, and the enzyme acted on this complex to produce free, luminescent luciferin, which was excreted and could be detected in the urine.

The investigators reported in the May 27, 2015, online edition of the journal *Science Translational Medicine* that *E. coli* Nissle 1917 robustly colonized tumor tissue in rodent models of liver metastasis after oral delivery but did not colonize healthy organs or fibrotic liver tissue. The microbial diagnostic generated a high-contrast urine signal through selective expansion in liver metastases (106-fold enrichment) and high expression of the lacZ reporter maintained by engineering a stable plasmid system. No deleterious health effects were detected in the mice more than 12 months after oral delivery.

The orally delivered bacteria did not accumulate in tumors all over the body, but did become established in nearly 90% of metastatic tumors in mice with colon cancer that had spread to the liver.

"We realized that if we gave a probiotic, we were not going to be able to get bacteria concentrations high enough to colonize the tumors all over the body, but we hypothesized that if we had tumors in the liver they would get the highest dose from an oral delivery," said senior author Dr. Sangeeta Bhatia, professor of health sciences, electrical engineering, and computer science, at the Massachusetts Institute of Technology. "There are interventions, like local surgery or local ablation, that physicians can perform if the spread of disease in the liver is confined, and because the liver can regenerate, these interventions are tolerated. New data are showing that those patients have a higher survival rate, so there is a particular need for detecting early metastasis in the liver."

Nanoparticle Packaging Dramatically Increases Potency of Anti-Cardiovascular Disease Drug

The use of biodegradable polymer nanoparticles to encapsulate a promising drug for treating atherosclerosis increased its residence time in the body of a treated mouse from less than one hour to at least four hours (and up to 48 hours or longer).

The drug, D-PDMP (D-Threo-1-phenyl-2-decanoylamino-3-morpholino-1-propanol), is a glycosphingolipid synthesis inhibitor. Previous studies had shown that it held considerable promise for the treatment of atherosclerosis and cardiac hypertrophy, but rapid in vivo clearance severely hindered its use in the clinical setting.

To overcome this impediment, investigators at Johns Hopkins University (Baltiomore, MD, USA; www.jhu.edu) sequestered D-PDMP inside a biodegradable polymer composed of polyethylene glycol (PEG) and sebacic acid (SA).

Some PEG-SA nanoparticles were labeled with PEG that contained a radioactive iodine tracer to allow in vivo bio-distribution and release kinetics of D-PDMP to be determined by using gamma-scintigraphy and subsequently, by mass spectrometry. Results published in the June 3, 2015, online edition of the journal *Biomaterials* revealed that polymer encapsulation increased the residence time of D-PDMP in the body of a treated mouse from less than one hour to at least four hours (and up to 48 hours or longer).

The substantially increased in vivo longevity provided by polymer encapsulation resulted in a 10-fold gain in the drug's efficacy for interfering with atherosclerosis and cardiac hypertrophy in a model based on mice genetically engineered to lack the gene for the apolipoprotein E receptor that were fed a high fat and high cholesterol diet.

"Our experiments illustrate clearly that while content is important, packaging can make or break a drug," said senior author Dr. Subroto Chatterjee, professor of medicine and pediatrics at Johns Hopkins University. "In our study, the right packaging vastly improved the drug's performance and its ability not merely to prevent disease but to mitigate some of its worst manifestations."

Treating Multiple Myeloma with the Patient's Own Marrow-Infiltrating Lymphocytes

Results of a small clinical trial support the feasibility of using a multiple myeloma patient's marrow-infiltrating lymphocytes (MILs) as the basis for adoptive T cell therapy (ACT).

Investigators at Johns Hopkins University (Baltimore, MD, USA; www.jhu.edu) hypothesized that MIL-based ACT in multiple myeloma could impart greater anti-tumor immunity in that they are obtained from the tumor microenvironment.

They discussed results from the first MILs ACT multiple myeloma clinical trial in the May 20, 2015, online edition of the journal *Science Translational Medicine*. For this study 22 patients with either newly diagnosed or relapsed disease had their MILs harvested, activated, and expanded with anti-CD3/CD28 beads plus interleukin-2, and subsequently re-infused on the third day following the standard regimen of high dose chemotherapy and stem cell transplant therapy.

Results revealed that seven patients experienced at least 90% reduction in tumor cell volume and survived, on average, 25.1 months without cancer progression. The remaining 15 patients had an average of 11.8 progression-free months following MILs therapy. Overall survival was 31.5 months for those with less than 90% disease reduction, while follow-up time is currently more than six years for those with a better response. None of the participants exhibited serious side effects from the MILs therapy.

"What we learned in this small trial is that large numbers of activated MILs can selectively target and kill myeloma cells," said senior author Dr. Ivan Borrello, professor of oncology at Johns Hopkins University. "Several US cancer centers have conducted similar experimental treatments, known as adoptive T cell therapy, but the Johns Hopkins team is apparently the only one to use MILs. Other types of tumor-infiltrating cells can be used, but they are usually less plentiful in patients' tumors and may not grow as well outside the body."

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REFERENCE STANDARDS
Horizon Discovery Group

The cell-free DNA (cfDNA) HDx Reference Standards support the development and optimization of cfDNA assays. They enable researchers to demonstrate the performance of their cfDNA assays by providing a reproducible, consistent, and reliable source of reference material.

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CHAMBERED COVERSLIP
ibidi

The µ-Slide 8 Well Grid-500 combines the µ-Slide 8 Well with the Grid-500, a laser-imprinted grid with a 500 µm repeat distance. The new µ-Slide is considered ideal for relocating and counting cells or cell clusters, with the sample observed through the polymer coverslip bottom.

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TRANSFECTION MEDIUM
Irvine Scientific

The BalanCD Transfectory CHO medium is for rapid, scalable production of recombinant proteins through transient transfection in CHO cells. It has been specifically designed to support sustained, high growth with increased transfection efficiency that can yield gram-scale protein expression.

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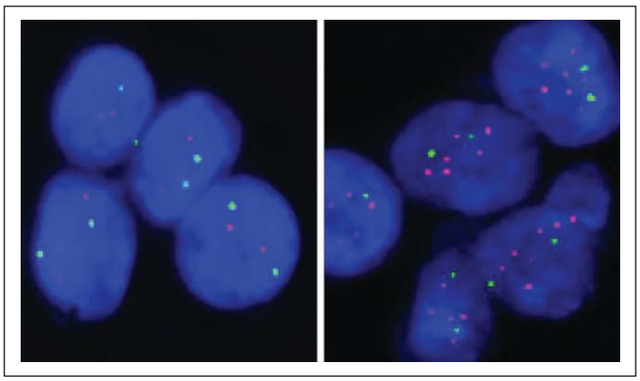
Newly-Identified Biomarker Indicates Risk of Breast Cancer Bone Metastasis



Cancer researchers have identified a gene that is critically linked to the ability of some breast cancer tumors to metastasize to the bone and which may be developed into a biomarker to identify patients at risk for this development.

There are currently no biomarkers for early breast cancer patient populations at risk of bone metastasis, which occurs in about 15%–20% of patients with estrogen-receptor-positive breast tumors. These tumors tend to metastasize to the bone, and represent 80% of all breast cancers.

Investigators at the Institute for Research in Biomedicine (Barcelona, Spain; www.irbbarcelona.org) analyzed more than 900 clinical samples of primary breast tumors while looking for genetic variations that favored bone metastasis.

They reported in the September 15, 2015, online edition of the *Journal of the National Cancer Institute* that patients with tumors in which the MAF (v-maf avian musculoaponeurotic fibrosarcoma oncogene homolog) gene was altered had a risk of metastasis to the bone that was 14 times higher than in those patients in which the gene was unaltered.

"This gene reliably predicts metastasis to the bone. Studying whether it is highly expressed in breast cancer patients to determine whether this also happens in a clinical setting is an important next step. It could improve the quality of life of these patients and the way clinicians manage their cancer. And this is exactly what we are doing," said senior author Dr. Roger Gomis, oncology group leader at the Institute for Research in Biomedicine.

The findings obtained in this study have led to the creation of the company Inbiomotion (Barcelona, Spain; http://inbiomotion.com), which has developed the tools necessary to begin clinical trials. An initial clinical trial will validate the use of the marker in some 3,300 patients.

Image: On left, breast cancer tumor cells negative for the bone metastasis marker, MFA. On right, breast cancer tumor cells positive for the marker (Photo courtesy of Gomis Laboratory, Institute for Research in Biomedicine, Barcelona).

New Genomic Research Kit Simplifies Exome Studies

An exciting new tool is now available for biotech researchers working in the field of genomic analysis.

The human exome is critical to our genetic make-up and is generally accepted as having the greatest influence on how the genetic blueprint is utilized. The exome is defined as all coding exons in the genome and is comprised of the most functionally relevant and best understood 1% of the human genome. Targeted sequencing is a powerful technique allowing researchers to focus their analysis on this critical portion of the genome.

Roche NimbleGen (Madison, WI, USA; www.nimblegen.com) has announced the release of its SeqCap EZ MedExome Target Enrichment Kit. This kit is a new exome solution that queries the entire human exome with enhanced coverage for exons of disease-associated gene regions. The design targets the genome assembly GRCh38/hg38 (coordinates for hg19 annotation are also available) with comprehensive sequencing coverage of medically relevant regions and protein coding regions. The product has been extensively optimized in design, empirical rebalancing, and manufacturing to increase coverage in hard-to-sequence regions for a more uniform and complete exome.

The SeqCap EZ MedExome kit produces greater than 85% on-target rate, demonstrates high uniformity across the targeted region with better than 98% sensitivity for SNP detection and greater than 99% specificity for SNP allele classification. Additionally, the SeqCap EZ MedExome kit is compatible with a mitochondria-specific design, which enables extended exome testing in cases where the mitochondria are of interest.

SeqCap EZ products enable a revolutionary process for the enrichment of selected genomic regions from full complexity human genomic DNA in a single step. Developed to eliminate the necessity of setting up thousands of PCR reactions, Sequence Capture allows for parallel enrichment of target regions in a single experiment.

"The release of the SeqCap EZ MedExome Target Enrichment Kit is an example of Roche Sequencing's commitment to further the evolution of genomic medicine," said Rebecca Selzer, president of Roche NimbleGen. "Immense interest in this design from our customers worldwide led to initiation of an early product evaluation process resulting in more than 40 evaluations across 11 countries globally prior to launch. This technology puts some of the most powerful tools of modern genomics to use in more laboratories around the world and is an invaluable asset in furthering the research of disease-associated mutations, while minimizing the need for costly retesting and follow-up sequencing."

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SINGLE-CHANNEL PIPETTE
Karl Hecht

The Capp Trio single-channel pipettes include three detachable volume knobs that allow users to change volume quickly by simply replacing the pre-calibrated knobs. The user-friendly pipettes are completely autoclavable, except for the knobs, and are considered ideal for routine lab work.

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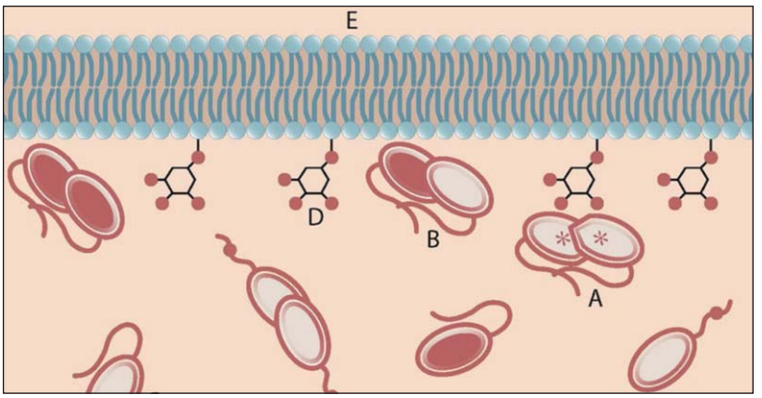
PTEN Requires a Stable Dimer Configuration to Effectively Suppress Tumor Growth



Molecular structural analysis has shown that the PTEN (phosphatase and tensin homolog) tumor suppressor can function effectively only when two wild-type alleles are present to form a stable dimer that can act on lipids in the cell membrane.

PTEN, which is missing in 60% to 70% of metastatic cancers in humans, is the name of a phospholipid phosphatase protein, and gene that encodes it. The PTEN gene acts as a tumor suppressor gene thanks to the role of its protein product in regulation of the cycle of cell division, preventing cells from growing and dividing too rapidly.

Due to difficulties in crystallizing the PTEN dimer, investigators at Carnegie Mellon University (Pittsburgh, PA, USA; www.cmu.edu) and a group of international collaborators used an advanced small-angle X-ray scattering (SAXS) technique to establish its structure in aqueous solution.

They reported in the August 20, 2015, online edition of the journal *Structure* that PTEN formed homodimers in vitro. To be fully functional, the C-terminal tails of the two proteins comprising the PTEN dimers had to bind the protein bodies in a cross-wise fashion, which made them more stable. As a result, they could more efficiently interact with the cell membrane, regulate cell growth, and suppress tumor formation.

Phosphorylation of the unstructured C-terminal tail of PTEN reduced PTEN activity, and this result was interpreted as a blockage of the PTEN membrane-binding interface through this tail. The results presented in this paper instead suggested that the C-terminal tail functioned in stabilizing the homodimer, and that tail phosphorylation interfered with this stabilization.

"Membrane-incorporated and membrane-associated proteins like PTEN make up one-third of all proteins in our body. Many important functions in health and disease depend on their proper functioning," said senior author Dr. Mathias Lösche, professor of physics and of biomedical engineering at Carnegie Mellon University. "Despite PTEN's importance in human physiology and disease, there is a critical lack of understanding of the complex mechanisms that govern its activity."

Image: An activated PTEN dimer that contains two non-mutant proteins (A) can transform the functional lipid (D) on the cellular membrane (E) into a chemical form that tunes down cancer predilection. Dimers that contain a mutated protein (B) or PTEN monomers cannot transform the functional lipid (Photo courtesy of Carnegie Mellon University).

Horizontal Laminar Flow Clean Bench for Process Protection

The laboratory equipment market now features a horizontal laminar flow clean bench that is billed as the ideal solution for Class 100 applications where process protection is needed. A typical application for the AirClean Systems (Creedmoor, NC, USA; www.aircleansystems.com) Horizontal Clean Bench laminar airflow workbench is inspection of parts or the assembly of optics that require a clean, particulate free environment. This laminar flow clean bench is constructed from polypropylene and features rear wall filtration, making it perfect for this and other critical applications and manipulations.

The horizontal clean bench is available in several sizes and can be placed on a bench top or a cart/stand. The UVTect Controller, which constantly monitors filter conditions and airflow, is standard on all horizontal clean benches. This system will alert the operator of insufficient airflow and required filter changes.

The AirClean Systems horizontal laminar flow bench provides a HEPA filtered airflow across the work area, and a particulate-free work surface. While an AirClean Systems tissue culture hood provides excellent process protection, it does not provide any personal protection from the application. AirClean Systems tissue culture hoods are not designed to be used for biological samples.

Image: The horizontal clean bench is available in several sizes and can be placed on a bench top or a cart/stand (Photo courtesy of AirClean Systems).

Novel Microreactor Enables Evaluation of Drug Toxicity on the Liver

A novel three-dimensional microreactor capable of maintaining metabolically active liver cells in vitro for over 28 days under stable oxygen gradients that mimic the in vivo microenvironment of the liver was used to determine why the painkiller acetaminophen (paracetamol) causes damage to this organ.

The liver tissue-based microreactor was the fruit of a project conducted by investigators at The Hebrew University of Jerusalem (Israel; www.huji.ac.il) and their colleagues at the Fraunhofer Institute for Cell Therapy and Immunology (Munich, Germany; www.fraunhofer.de). The device was capable of maintaining the growth of liver cells under carefully controlled conditions for up to 28 days. Mitochondrial respiration was monitored using two-frequency phase modulation of phosphorescent microprobes embedded in the tissue. Phase modulation is focus independent and unaffected by cell death or migration.

The investigators reported in the June 4, 2015, online edition of the journal *Archives of Toxicology* that the device enabled the sensitive measurement of oxygen dynamics that revealed important information on the drug mechanism of action and transient subthreshold effects. Exposure to the widely used analgesic acetaminophen caused an immediate, reversible, dose-dependent loss of oxygen uptake followed by a slow, irreversible, dose-independent death. Transient loss of mitochondrial respiration was also detected below the threshold of acetaminophen toxicity.

It had been thought that liver toxicity was linked to acetaminophen's toxic byproduct NAPQI (N-acetyl-p-benzoquinone imine), which is normally produced only in small amounts and then almost immediately detoxified in the liver. However, under some conditions in which NAPQI is not effectively detoxified (usually in case of acetaminophen overdose), it causes severe damage to the liver. This becomes apparent three to four days after ingestion and may result in death from fulminant liver failure several days after the overdose. Results obtained with the liver bioreactor demonstrated the importance of tracing toxicity effects over time and suggested that NAPQI-independent targeting of mitochondrial complex III might be responsible for acetaminophen toxicity.

"The liver organs we created were less than a millimeter in diameter and survive for more than a month," said senior author Dr. Yaakov Nahmias, professor of bioengineering at The Hebrew University of Jerusalem. "We realized that because we are building the organs ourselves, we are not limited to biology, and could introduce electronic and optical sensors to the tissue itself. Essentially we are building bionic organs on a chip. Because we placed sensors inside the tissue, we could detect small and fast changes in cellular respiration that nobody else could. Suddenly nothing we saw made sense."

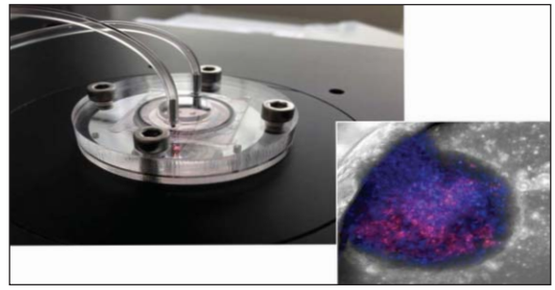


Image: The liver-on-chip device and a microscopic image of a bionic liver (Photo courtesy of Dr. Yaakov Nahmias, the Hebrew University of Jerusalem).

Method for In Vitro Neuron Culture to Advance Serotonin Research

A method has been developed that enables human serotonin-producing neurons, generated from transformed fibroblasts, to be grown in culture for use as a tool for research and drug discovery on many serotonin-related mental disorders.

Serotonergic (5HT) neurons exert diverse and widespread functions in the brain. Malfunctions of the serotonergic system give rise to a variety of mental illnesses including depression, anxiety, obsessive-compulsive disorder, autism, and eating disorders. Up to now, it has not been possible to grow cultures of human serotonin-producing neurons in the laboratory, so studies have been carried out on animals.

A technological breakthrough devised by researchers at the University at Buffalo (NY, USA; www.buffalo.edu) has changed this picture. They demonstrated a method for directly converting human primary fibroblasts into induced serotonergic (i5HT) neurons. This was accomplished by growing fibroblasts in medium to which the genes for the proteins Ascl1 (Achaete-scute homolog 1), Foxa2 (forkhead box protein A2), Lmx1b (LIM homeobox transcription factor 1-beta), and FEV (a gene exclusively expressed in neurons of the central serotonin (5-HT) system) had been added. The transformation process was enhanced by inhibiting the gene for p53 and maintaining appropriate culture conditions including hypoxia.

Results published in the July 28, 2015, online edition of the journal *Molecular Psychiatry* revealed that the i5HT neurons expressed markers for mature serotonergic neurons, had calcium ion dependent 5HT release and selective 5HT uptake, exhibited spontaneous action potentials and spontaneous excitatory postsynaptic currents. Application of serotonin significantly increased the firing rate of spontaneous action potentials, demonstrating the functional utility of i5HT neurons for studying serotonergic neurotransmission.

"This research shows that it is possible to convert one type of cell into other types that have been difficult to access, such as neurons or heart cells," said senior author Dr. Jian Feng, professor of physiology and biophysics at the University at Buffalo. "All we need to do is find out the combination of transcription factors that is necessary. Sooner or later, we will find out what those combinations are so that we can regenerate cells and eventually tissues that will mimic the real cells and tissues in the body."

"These patient-specific serotonin neurons will be very useful to the discovery of new drugs for diseases ranging from depression and anxiety to obsessive-compulsive disorder and many others," said Dr. Feng. "They will not only allow researchers to study why certain individuals develop a disease but also to find out what can be done to treat it."

Nucleoside Supplementation Reduces Genomic Damage in Induced Pluripotent Stem Cells

Spanish researchers have described a method to reduce the amount of genomic damage incurred during the process that transforms mature adult cells into induced pluripotent stem cells (iPSC), thereby making them potentially useful for biomedical applications.

The reasons behind the genomic instability observed in iPSCs remain mostly unknown. Investigators at the Spanish National Cancer Research Center (Madrid, Spain; www.cnio.es) recently suggested that this genomic instability was similar to the phenomenon of oncogene-induced replication stress, and that the expression of reprogramming factors induced replication stress.

Replication stress is defined as slowing or stalling in DNA replication fork progression. It arises from many different sources, which are considered as replication barriers such as telomeres, repetitive sequences, DNA lesions and misincorporation of ribonucleotides, secondary DNA structures, DNA–RNA hybrids, dormant replication origins, collisions between replication and transcription complexes, hypo-acetylation and compaction of chromatin, early-replicating fragile sites (ERFSs) and common fragile sites (CFSs). Overexpression or constitutive activation of oncogenes has been cited as an emerging source of replication stress.

The Spanish investigators reported in the August 21, 2015, online edition of the journal *Nature Communications* that increasing the levels of the protein checkpoint kinase 1 (CHK1) reduced reprogramming-induced replication stress and increased the efficiency of iPSC generation. Similarly, nucleoside supplementation during reprogramming reduced the load of DNA damage and genomic rearrangements during the iPSC generation process. The data revealed that lowering replication stress during reprogramming, genetically or chemically, provided a simple strategy to reduce genomic instability in mouse and human iPSCs.

First author Dr. Sergio Ruiz, a researcher in the genomic instability group at the Spanish National Cancer Research Center, said, "Based on previous research performed by the group, we knew that an additional input of nucleoside reduces replication stress, probably by facilitating the successful replication of DNA as it increases the rate of cell division during the reprogramming process."

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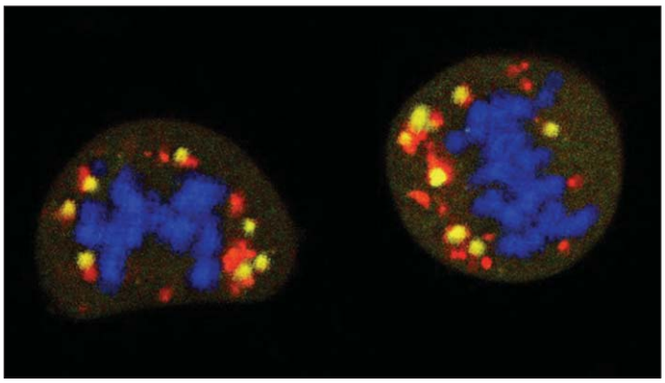
Blocking Glycolysis Improves Effect of Antimitotic Chemotherapeutic Drugs



Blocking the attempts of tumor cells to establish glycolysis as their primary means of generating energy was found to significantly augment the chemotherapeutic benefits of drugs that prevent the cells from dividing.

Cancer researchers have long wondered how tumor cells survived when their ability to divide was disrupted by treatment with antimitotic drugs such as the toxanes (paclitaxel and docetaxel) or alkaloids derived from Vinca (*Catharanthus roseus*), such as vinblastine, vincristine, and vinorelbine.

Investigators at the Spanish National Cancer Research Center (Madrid, Spain; www.cnio.es) were among groups looking into this question. They reported in the August 31, 2015, online edition of the journal *Nature Cell Biology* that survival during mitotic arrest was affected by the special energetic requirements of mitotic cells. Prolonged mitotic arrest resulted in mitophagy-dependent loss of mitochondria, accompanied by reduced ATP levels and the activation of AMPK (5' adenosine monophosphate-activated protein kinase).

Oxidative respiration in cells undergoing mitotic arrest was replaced by glycolysis owing to AMPK-dependent phosphorylation of PFKFB3 (6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3) and increased production of this protein as a consequence of mitotic-specific translational activation of its mRNA. Induction of autophagy or inhibition of AMPK or PFKFB3 resulted in enhanced cell death in mitosis and improved the anticancer efficiency of chemotherapeutic agents (microtubule poisons) in breast cancer cells.

"The therapeutic value of inhibiting PFKFB3 has often been discussed; however, no appropriate cell-based scenario had been proposed for its clinical use. Our results suggest that PFKFB3 inhibitors can be extremely efficient in combination with antimitotic drugs," said senior author Dr. Marcos Malumbres, head of the cell division and cancer group at the Spanish National Cancer Research Center.

Image: During the process of cell division, the mitochondria are damaged (yellow indicator) making the cells particularly dependent on glucose as a source of energy. Genetic material is shown in blue and mitochondria in red (Photo courtesy of the Spanish National Cancer Research Center).

Blocking the MicroRNA That Controls Angiogenesis Slows Breast Tumor Growth in a Diabetic Mouse Model

A team of molecular biologists demonstrated that it was possible to inhibit growth of breast tumors in a diabetic mouse model by injecting the animals with an antagonist of the microRNA (miRNA) that controls the process of angiogenesis (formation of new blood vessels).

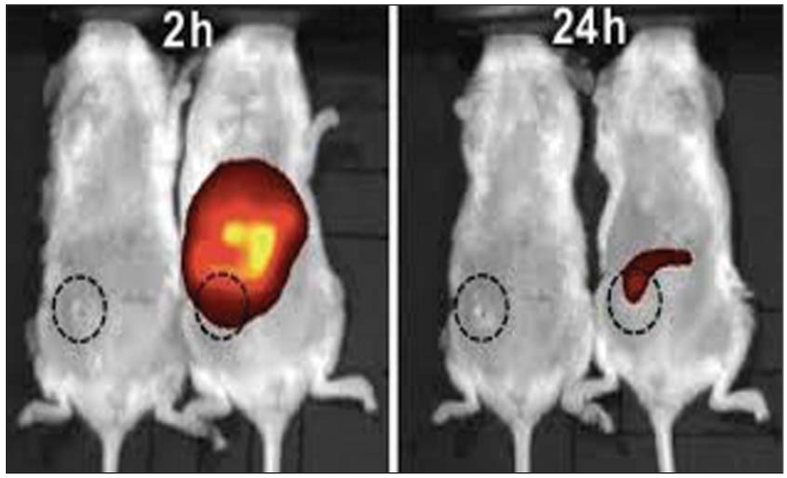
Investigators at the Cleveland Clinic (OH, USA; www.clevelandclinic.org) had reported previously that angiogenesis in response to hyperglycemia in a cell- and tissue-specific manner was regulated by a novel pathway under the control of the microRNA miR-467. A microRNA is a member of the class of RNA fragments about 20 nucleotides long that block gene expression by attaching to molecules of messenger RNA (mRNA) in a fashion that prevents them from transmitting the protein synthesizing instructions they had received from the DNA.

In the current study, the investigators examined whether systemic administration of an antagonist of miR-467 would prevent hyperglycemia-induced local angiogenesis in a tissue-specific manner. To this end they studied the effect of the antagonist on hyperglycemia-induced tumor growth and angiogenesis and on skin wound healing in mouse models of diabetes.

They reported in the September 2015 issue of the *FASEB Journal* that the systemic injection of the antagonist prevented hyperglycemia-induced angiogenesis and growth of mouse and human breast cancer tumors, where the miR-467 pathway was active in hyperglycemia. In tissues where the miR-467–dependent mechanism was not activated by hyperglycemia, there was no effect of the antagonist: the systemic injection did not affect skin wound healing or the growth of prostate tumors. The antagonist did not have any effect on organs or tissues unaffected by increased blood vessel growth.

"Complications of diabetes are the main reason for mortality and hospitalization of diabetic patients. The advanced methods of measuring and regulation of the blood sugar levels resulted in deaths from diabetic coma being very rare, but the vascular complications remain an important problem that leads to mortality and loss of quality of life," said Dr. Olga Stenina-Adognravi, a researcher in the department of molecular cardiology at the Cleveland Clinic. "Developing a new organ-specific way to prevent and treat the vascular complications and cancer growth in diabetic patients is the goal of our work."

Acid-Sensitive Nanoparticle Drug Delivery System Targets Cancer Stem Cells



A novel nanoparticle-based drug delivery system was designed to destroy the cancer stem cells that are responsible for tumor recurrence and development of drug resistance. Drug resistant cancer stem-like cells are responsible for cancer recurrence associated with conventional chemotherapy. To target this class of cells, investigators at The Ohio State University (Columbus, USA; www.osu.edu) developed a novel type of doxorubicin (DOX)-encapsulated polymeric nanoparticles.

Although in use for more than 40 years as a primary chemotherapy drug, DOX is known to cause serious heart problems. To prevent these, doctors may limit the amount of DOX given to each patient so that the total amount a patient receives over her or his entire lifetime is 550 milligrams per square meter, or less. Furthermore, the necessity to stop treatment to protect the patient from heart disease may diminish the usefulness of DOX in treating cancer.

The surface of the DOX nanoparticles was "decorated" with chitosan, a natural polysaccharide that guided the particles to the CD44 receptors on the cancer stem cells.

Chitosan is muco-adhesive in nature, reactive (so it can be produced in many different forms), and has a positive charge under acidic conditions. This positive charge comes from protonation of its free amino groups. Lack of a positive charge means chitosan is insoluble in neutral and basic environments. However, in acidic environments, protonation of the amino groups leads to an increase in solubility. The implications of this are very important to biomedical applications. This molecule will maintain its structure in a neutral environment, but will solubilize and degrade in an acidic environment. This means chitosan can be used to transport a drug to an acidic environment, such as the tumor microenvironment, where the chitosan packaging will then degrade, releasing the drug.

Results published in the May 25, 2015, online edition of the journal *ACS Nano* revealed that the nanoparticle design strategy increased the apparent cytotoxicity of doxorubicin by six times in comparison to the use of the free drug for eliminating CD44+ cancer stem-like cells residing in cultured three-dimensional mammary tumor spheroids. They further showed that the nanoparticles reduced the size of tumors in a mouse orthotopic xenograft tumor model with no evident systemic toxicity.

The investigators concluded that further development of the nanoparticle system to target cancer stem-like cells with low systemic toxicity could provide a new treatment arsenal for improving the survival of cancer patients.

Image: After two hours, doxorubicin-carrying nanoparticles accumulated in cancer cells (red and yellow) in mice (left) and destroyed most of the tumor within a day (right) (Photo courtesy of the ACS).

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INVERTED MICROSCOPE
Olympus

The CKX53 is a next-generation inverted microscope designed for fast, efficient cell culture checking and documentation. The CKX53's advanced imaging capabilities and user-friendly design reduce operator fatigue and improve cell culture throughput.

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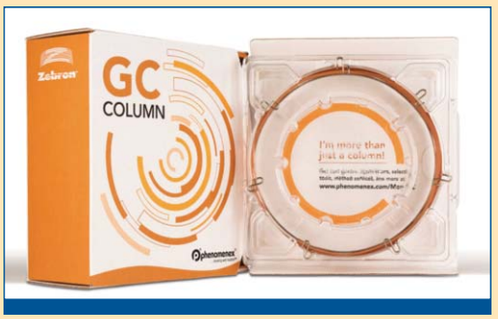
GC COLUMN
Phenomenex



The Zebron ZB-5MSPLUS is designed for separations in industries such as pharmaceutical/clinical research, forensic toxicology and industrial chemicals. It eliminates active sites on the column's surface that can negatively affect peak shapes for challenging compounds.

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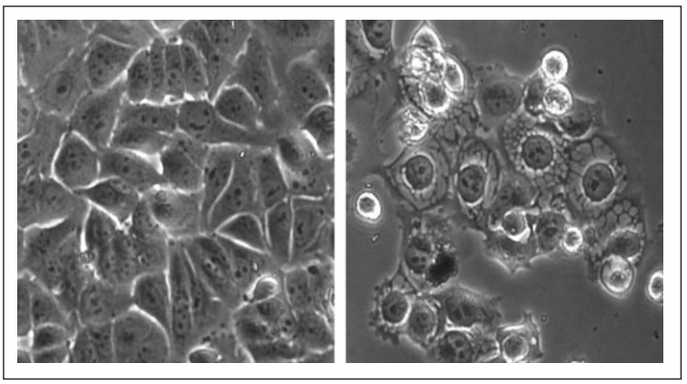
Drug Candidate Propels Cancer Cells into Fatal Overdrive



A candidate drug that destroys cancer cells by stimulating them to produce more proteins than the cells can actually process was shown to kill a wide variety of cancer cells in culture and to inhibit tumor growth in animal models.

Investigators at Baylor College of Medicine (Houston, TX, USA; www.baylor.edu) identified the drug MCB-613 as an activator of the steroid receptor coactivators (SRC-1, SRC-2, and SRC-3) while screening a large number of compounds for drugs that would inhibit SRCs. However, when the investigators tested the compound with cultures of cancer cells, they found that MCB-613 could super-stimulate SRCs' transcriptional activity. Further study revealed that MCB-613 increased SRCs' interactions with other coactivators and markedly induced ER (endoplasmic reticulum) stress coupled to the generation of toxic reactive oxygen species (ROS).

Results published in the August 10, 2015, issue of the journal *Cancer Cell* revealed that MCB-613 killed human breast, prostate, lung, and liver cancer cells, while sparing normal cells. When administered to 13 mice with breast cancer, MCB-613 reduced tumor growth without causing toxicity, whereas tumors continued to grow by about threefold over seven weeks in the control group of 14 mice. The toxic effect of the drug was shown to be due to the accumulation of unfolded proteins in the ER. The inability of the ER to cope with such a large number of proteins caused a state of stress to develop that stimulated production of toxic ROS species and the destruction of the cell.

"No prior drug has been previously developed or proposed that actually stimulates an oncogene to promote therapy," said contributing author Dr. David Lonard, associate professor of molecular and cell biology at Baylor College of Medicine. "Our prototype drug works in multiple types of cancers and encourages us that this could be a more general addition to the cancer drug arsenal."

Image: Cancer cells treated with a control (left) and the overstimulating compound MCB-613 (right) (Photo courtesy of Dr. Lei Wang, Baylor University College of Medicine).

Mutation Predicts Response of Breast Cancer to Treatment with Drug Duo

A gene mutation was identified as a biomarker that can predict whether a patient with HER-2 positive breast cancer will respond positively to the most effective dual anti-HER2 treatment.

Recent evidence has shown that the PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha) gene was mutated in a range of human cancers. It has been found to be oncogenic and has been implicated in cervical cancers.

The phase II CHER-LOB (Chemotherapy, Herceptin, and Lapatinib in Operable Breast Cancer) study found in 2012 that the combination of trastuzumab plus lapatinib, added to neoadjuvant chemotherapy, was more effective than either agent alone. The CHER-LOB study was a noncomparative, randomized, phase II trial of preoperative taxane-anthracycline in combination with trastuzumab, lapatinib, or combined trastuzumab plus lapatinib in patients with human epidermal growth factor receptor 2 (HER2)-positive, stage II to IIIA operable breast cancer.

In a follow-up to the CHER-LOB study, investigators at Istituto Oncologico Veneto IRCCS (Padua, Italy, www.ioveneto.it) sought to identify biomarkers that would indicate which patients would benefit most (or least) from treatment with the trastuzumab plus lapatinib combination of chemotherapeutic drugs.

To this end they carried out genomic analyses on fresh-frozen tissue samples from 121 breast cancer patients positive for human epidermal growth factor 2 (HER2) who had been treated randomly with neoadjuvant chemotherapy plus trastuzumab, lapatinib, or both trastuzumab and lapatinib. Pre- and post-treatment samples were centrally evaluated for HER2, p95-HER2, phosphorylated AKT (pAKT), phosphatase and tensin homolog, Ki67, apoptosis, and PIK3CA mutations.

Results published in the August 5, 2015, online edition of the journal the *Oncologist* revealed that only 12.5% of patients with mutated PIK3CA responded to treatment with trastuzumab plus lapatinib, while the response rate to dual anti-HER2 therapy was four-times higher among patients with normal PIK3CA (48.4%). Thus, PIK3CA mutation could be a potential predictive marker of resistance to dual anti-HER2 treatment that should be further studied in breast cancer.

"We are seeing more and more anti-HER2 treatments becoming available to treat patients with HER2-positive breast cancer," said senior author Dr. Pierfranco Conte, professor of medicine at Istituto Oncologico Veneto IRCCS. "By identifying new markers that help us to predict which patients are more sensitive to which anti-HER2 treatments, we are moving closer to treatment personalization."

Mathematical Models Guide Microliter Doses of Drugs to Specific Pathological Sites in the Lungs

A recent paper described a novel technique for precise delivery of microliter quantities of drugs directly to selected pathological areas in the lungs.

In order to treat lung diseases such as cystic fibrosis, bronchopneumonia, chronic obstructive pulmonary disease, and lung cancer, drugs are administered in a systemic fashion, either orally or by aerosol inhalation. Large amounts of the drug have to be given in order to achieve therapeutic levels at the pathological site, and these doses may cause adverse effects to other organs in the body.

Investigators at Columbia University (New York, NY, USA; www.columbia.edu) reported in the August 31, 2015, online edition of the journal *Proceedings of the National Academy of Sciences of the United States of America (PNAS)* that they had developed a method for the precise delivery of drugs to a designated area of the lungs, which would lower the required dosage and reduce unwanted side effects.

Their method utilized a soluble liquid plug of very small volume (less than one milliliter) that was instilled into the upper airways. Programmed air ventilation of the lungs was employed to push the plug into a more distal airway to achieve deposition of liquid film onto the lung epithelium at a precisely determined location. The plug volume and ventilation conditions were determined by mathematical modeling of plug transport in a tubular geometry.

The investigators used three different in vivo imaging methods to demonstrate the application of targeted liquid film deposition to the lungs of animals in a rat model system. These results suggests that instillation of microvolumes of liquid into a ventilated pulmonary airway could be an effective strategy to deliver exact doses of drugs to targeted pathologic regions of the lung, especially those inaccessible by bronchoscopy. Using this method increased the in situ efficacy of the drug while minimizing any systemic side effects.

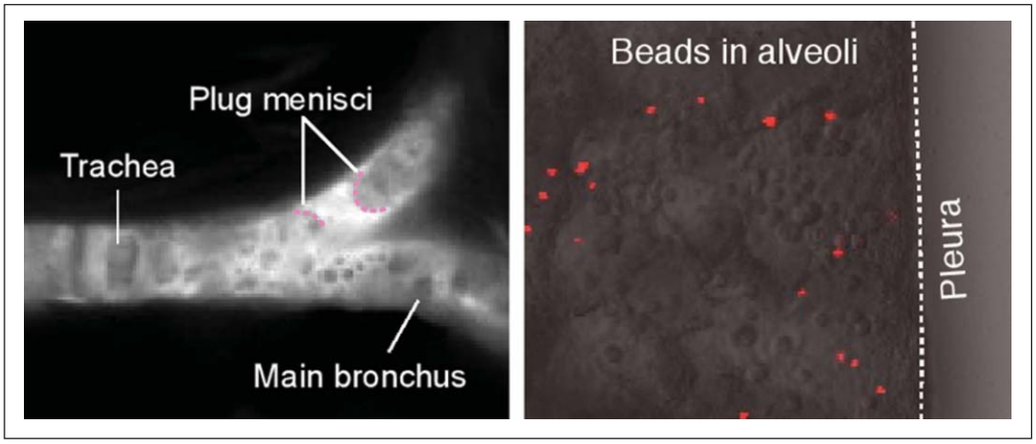


Image: A small liquid plug in the bronchus was manipulated by air ventilation to deliver a drug into the most distant alveoli (Photo courtesy of Dr. Jinho Kim, Columbia University).

"We envision that our micro-volume liquid instillation approach will enable predictable drug concentrations at the target site, reducing the amount of drug required for effective disease treatment with significantly reduced side effects," said senior author Dr. Gordana Vunjak-Novakovic, professor of biomedical engineering and of medical sciences at Columbia University. "We are fascinated by the opportunities that bioengineering approaches offer to more effectively treat lung disease. The lung is a hugely complex organ that has billions of cells within a hierarchically organized tissue that cannot be built from scratch. Four years ago, we started research of lung regeneration using stem cells and bioengineering methods. And we continue to work with our clinical colleagues to develop new treatment approaches for treating lung disease."

Nanoparticle-Augmented Spectroscopy Reveals Structure Of Alzheimer's Peptide

The use of lipid bilayer-encapsulated silver nanoparticles to increase the sensitivity of a Raman spectroscopy technique allowed researchers to determine the structure of Alzheimer's disease-related membrane-attached oligomers of amyloid-beta40 (Abeta40) peptide.

Raman spectroscopy exploits the inelastic scattering (so-called "Raman" scattering) phenomena to detect spectral signatures of important disease progression biomarkers, including lipids, proteins, and amino acids. In a novel modification of the Raman technique, investigators at the Tata Institute of Fundamental Research (Mumbai, India; www.tifr.res.in) and the University of Toronto (Canada; www.utoronto.ca) introduced a surface enhanced Raman spectroscopy technique that could determine the conformation of membrane-bound proteins, at low micromolar concentrations, and also in the presence of a substantial membrane-free fraction. Unlike conventional surface enhanced Raman spectroscopy, this approach did not require immobilization of molecules, as it used spontaneous binding of proteins to lipid bilayer-encapsulated silver nanoparticles.

The investigators applied this technique to probe the structure of membrane-attached oligomers of amyloid-beta40 (Abeta40), whose conformation is needed to explain certain aspects of Alzheimer's disease.

They reported in the August 25, 2015, online edition of the journal *ACS Nano* that isotope-shifts in the Raman spectra helped them to obtain secondary structure information at the level of individual residues. Results showed the presence of a beta-turn, flanked by two beta-sheet regions. The investigators then used solid-state NMR data to confirm the presence of the beta-sheets in these regions. In the membrane-attached oligomer, they found a strongly contrasting and near-orthogonal orientation of the backbone H-bonds compared to what is found in the mature, less-toxic Abeta fibrils.

Contributing author Dr. Gilbert Walker, professor of chemistry at the University of Toronto, said, "While the amyloid beta got fooled by the fat layer-encased silver nanoparticles that mimicked the outer membranes of living cells and stuck to the membrane, the silver inside enhanced the signal to a measurable level and acted as a light beacon to reveal the peptide signature."

"Everybody wants to make the key to solve Alzheimer's disease, but we do not know what the lock looks like. We now have a glimpse of something, which could be the lock. May be it is still not the real thing, but as of now, this is our best bet," said senior author Dr. Sudipta Maiti, professor of chemical sciences at the Tata Institute of Fundamental Research.

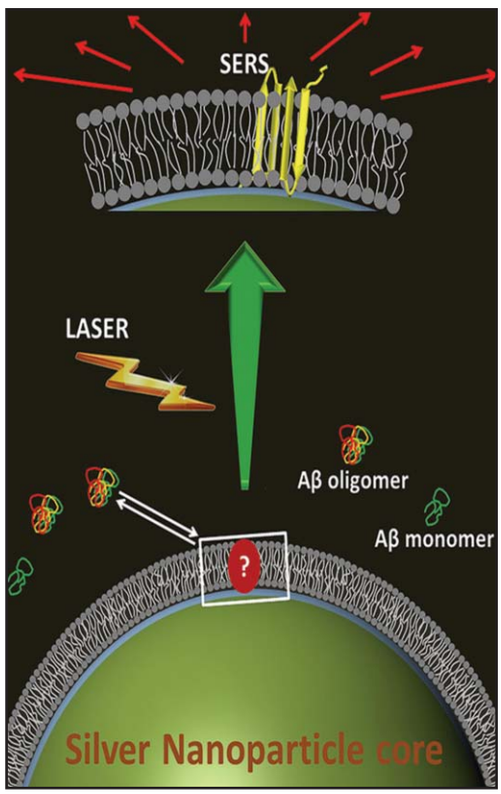


Image: Toxic Alzheimer's amyloid beta molecules landing on a fake cell membrane, wrapped around a silver nanoparticle. A laser, with help from the silver particle, lights up the molecule to reveal its structure (Photo courtesy of Dr. Debanjan Bhowmik, Tata Institute of Fundamental Research).

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The Flexsafe 3D Pre-designed Solutions (PDS) are intended for the storage and shipping of biopharmaceutical fluids, and meet all the functional and validation requirements of the biopharmaceutical industry. The single-use bags are available in a range of sizes from 50L to 1,000L.

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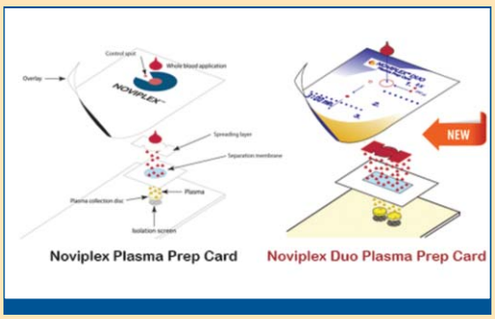

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The NanoDrop One features a high-resolution, touch screen interface, and auto-range technology that provides accurate measurements for concentrated samples with no dilutions. It measures 1-2 µL of sample in seconds without cuvettes, making it a cost- and time-effective solution for busy labs.

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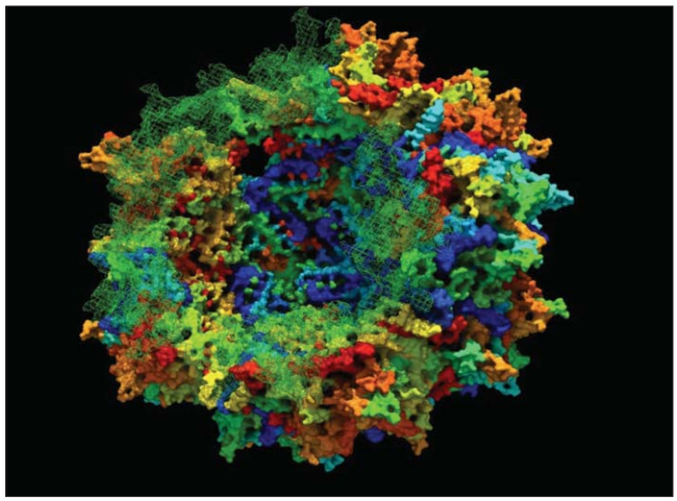
Ancient Viruses Built from Computer Models May Improve Gene Therapy Delivery



An advanced computer modeling strategy was used to design ancient forms of adeno-associated viruses (AAVs), which were then synthesized in the laboratory for use as potential delivery vectors for gene therapy.

AAV vectors have emerged as a gene-delivery platform with demonstrated safety and efficacy in a handful of clinical trials for monogenic disorders. However, limitations of the current generation of vectors – including rejection by the patient's immune system – often prevent broader application of AAV gene therapy. Efforts to engineer AAV vectors have been hampered by a limited understanding of the structure-function relationship of the complex multimeric icosahedral architecture of the particle.

To bypass these limitations investigators at Harvard University Medical School (Boston, MA, USA; www.harvard.edu) built computer models of the AAC viral capsid using ancestral sequence reconstruction from inferred evolutionary intermediates. Computer model-derived sequences were synthesized in the laboratory and characterized for biological properties relevant to clinical applications.

Results published in the July 30, 2015, online edition of the journal *Cell Reports* described the generation of nine functional putative ancestral AAVs and the identification of Anc80, the predicted ancestor of the widely studied AAV serotypes 1, 2, 8, and 9, as a highly potent in vivo gene therapy vector for targeting liver, muscle, and retina.

"The vectors developed and characterized in this study demonstrate unique and potent biology that justify their consideration for gene therapy applications," said senior author Dr. Luk H. Vandenberghe, professor of ophthalmology at Harvard University Medical School. "We believe our findings will teach us how complex biological structures, such as AAVs (adeno-associated viruses), are built. From this knowledge, we hope to design next-generation viruses for use as vectors in gene therapy."

Image: An artist's conception of an adeno-associated viral capsid in formation by ancestral sequence reconstruction (Photo courtesy of Dr. Eric Zinn, Harvard University Medical School).

Monkeys Protected from MERS Infection by Synthetic DNA Vaccine

A synthetic DNA vaccine directed against the Middle East Respiratory Syndrome's (MERS) spike protein was found to completely protect rhesus macaques from developing pneumonia after having been exposed to the live virus.

MERS is caused by an emerging human coronavirus, which is distinct from the severe acute respiratory syndrome coronavirus (SARS-CoV), and represents a novel member of the lineage C betacoronoviruses. Since its identification in 2012, MERS coronavirus (MERS-CoV) has been linked to more than 1372 infections manifesting with severe morbidity and, often, mortality (about 495 deaths) in the Arabian Peninsula, Europe, and, most recently, the United States. During a recent outbreak in South Korea that infected more than 181 people and caused more than 30 deaths, rapid human-to-human transmission was documented with in-hospital transmission the most common route of infection.

Investigators at the University of Pennsylvania (Philadelphia, USA; www.upenn.edu) and colleagues from several other research institutions reported in the August 19, 2015, online edition of the journal *Science Translational Medicine* that they had developed a synthetic DNA vaccine against MERS-CoV. An optimized DNA vaccine encoding the MERS spike protein induced potent cellular immunity and antigen-specific neutralizing antibodies in mice, macaques, and camels.

Vaccinated rhesus macaques seroconverted rapidly and exhibited high levels of virus-neutralizing activity. Upon MERS viral challenge, all of the monkeys in the control-vaccinated group developed characteristic disease, including pneumonia. Vaccinated macaques were protected and failed to demonstrate any clinical or radiographic signs of pneumonia.

Results presented in this paper demonstrate that a consensus MERS spike protein synthetic DNA vaccine can induce protective responses against viral challenge, indicating that this strategy may have value as a possible vaccine modality against this emerging pathogen.

"The significant recent increase in MERS cases, coupled with the lack of effective antiviral therapies or vaccines to treat or prevent this infection, have raised significant concern," said senior author Dr. David B. Weiner, professor of pathology and laboratory medicine at the University of Pennsylvania. "Accordingly the development of a vaccine for MERS remains a high priority."

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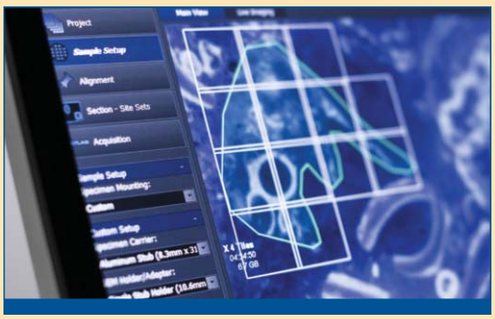

The Atlas 5 hardware/software package extends the capacity of ZEISS SEMs and focused ion beam SEMs. It streamlines automatic image acquisition and lets users benefit from its efficient navigation and correlation of images from any source including light and X-ray microscopes.

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SAMPLE SCANNER
Ziath

The DataPaq Cube reader provides users with a fast and flexible system for scanning 2D barcoded tubes housed in both SBS and cryobox formats. It works with all currently available rack types and can scan and decode a 96-tube rack in less than two seconds using standard computer hardware.

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Modular Cooling/Heating System Safeguards Temperature-Sensitive Biological Samples

A new modular system designed for precise, controlled cooling and heating of biological samples in microplates, vials and Eppendorf tubes is now available for biotech, clinical, and life science laboratories.

The ChilliBlock from Asynt (Isleham, United Kingdom; www.asynt.com) is a modular system designed for both heating and cooling. The ChilliBlock tube blocks are manufactured from clear, resistant, anodized aluminum. The base unit easily attaches to most laboratory heating cooling circulators, enabling precise, stable, and even temperature control of biological samples from -30 to +160 degrees Celsius.

The ChilliBlock's low profile makes it compatible with most robotic platforms, but it can also be used as a stand-alone system. ChilliBlock has interchangeable blocks for tubes, vials, and plates but custom sizes are also available. The tube plate also offers cap holding for Eppendorf tubes.

ChilliBlock is not for use on an active heating/cooling plate but can be used with an ice bath or simply pre-cooled for use directly on the lab bench. The ChilliBlock cooling base is insulated to ensure performance, temperature homogeneity and to reduce ice formation.

The Asynt ChilliBlock enables stable, consistent temperature control (+/- 0.1 degree Celsius) of biological samples in a wide range of standard and custom formats.

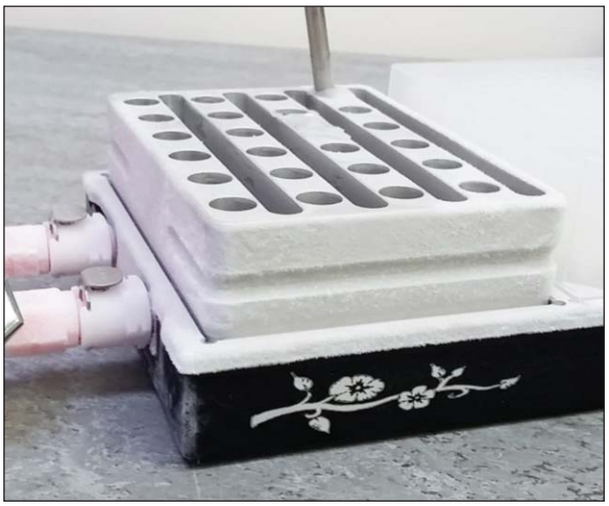


Image: The ChilliBlock modular system for precise, controlled cooling and heatingof biological samples (Photo courtesy of Asynt).

Plant Extract Prevents Bacterial Skin Infections by Disrupting Quorum Sensing

An extract prepared from the leaves of the European chestnut *Castanea sativa*, a stalwart of Mediterranean region folk medicine, has been found to efficiently block the virulent effects of *Staphylococcus aureus* by preventing toxin production rather than by killing the organism.

Research on medical folklore in several Mediterranean countries led investigators from Emory University (Atlanta, GA, USA; www.emory.edu) to the European chestnut. Extracts from the leaves of this plant had long been used by locals to wash their skin as a treatment for skin infections and inflammations.

In the laboratory, the investigators evaluated the extract for ability to block *Staphylococcus aureus* infection and ultimately identified more than 94 compounds. One fraction, enriched with derivatives of the triterpenes ursene and oleanene, was found to be particularly effective in preventing *S. aureus* infection while not actually killing the bacteria.

The investigators found that this fraction actually blocked the organism's quorum sensing inhibitory activity. Quorum sensing is a mechanism used by pathogenic bacteria not only to modulate virulence factor production but also to adapt to the metabolic demands of living in communities. Quorum-sensing systems have been shown to be key virulence regulators in both gram-negative and gram-positive pathogens. It has been suggested that quorum sensing represents a novel target for the development of agents to treat or prevent bacterial infections.

Results published in the August 21, 2015, online edition of the journal *PLOS ONE* presented evidence of the extract's *Staphylococcus aureus* accessory gene regulator (agr) allele blocking activity, as measured in toxin outputs, reporter assays hemolytic activity, cytotoxicity studies, and an in vivo abscess model. The results demonstrated the extract's lack of cytotoxicity to human keratinocytes and murine skin, as well as lack of growth inhibitory activity against *S. aureus* and a panel of skin commensals. In addition, they showed that serial growth of the bacteria in the presence of the extract did not result in acquisition of resistance to the quorum quenching effect.

"We were able to trace out the pathways in the lab, showing how our botanical extract blocks quorum sensing and turns off toxin production entirely," said first author Dr. Cassandra Quave, assistant professor of biology at Emory University. "Many pharmaceutical companies are working on the development of monoclonal antibodies that target just one toxin. This is more exciting because we have shown that with this extract, we can turn off an entire cascade responsible for producing a variety of different toxins."

"We have identified a family of compounds from this plant that have an interesting medicinal mechanism," said Dr. Quave. "Rather than killing staph, this botanical extract works by taking away staph's weapons, essentially shutting off the ability of the bacteria to create toxins that cause tissue damage. In other words, it takes the teeth out of the bacteria's bite. It is easy to dismiss traditional remedies as old wives' tales, just because they do not attack and kill pathogens, but there are many more ways to help cure infections, and we need to focus on them in the era of drug-resistant bacteria."

Bone Marrow Transplantation Techniques Are Successfully Adapted for Lung Repair

A new approach for repairing the damage caused to lung tissue by diseases such as emphysema, bronchitis, asthma, and cystic fibrosis is based on transplanting embryonic stem cells into damaged lungs that have been conditioned by radiation treatment.

Investigators at the Weizmann Institute of Science (Rehovot, Israel; www.weizmann.ac.il) recognized the similarity between the arrangement of cellular compartments within the lung and the arrangement of similar compartments in the bone marrow. They reasoned that methods used for bone marrow transplantation might prove useful for inducing stem cells to mature into functional lung tissue.

Initial experiments indicated that human and mouse embryonic lung tissue from the canalicular stage of development (20–22 weeks of gestation for humans, and embryonic day 15–16 for the mouse) were enriched with stem cell progenitors residing in distinct niches. Younger cells had not yet completed the process of differentiation, while older cells were less capable of lung regeneration.

The investigators exposed naphthalene-injured, lung damaged mice to doses of sublethal radiation to empty out lung progenitor niches and to reduce stem cell competition. A single cell suspension of canalicular lung tissue of either mouse or human fetal origin was then administered intravenously.

Results published in the July 13, 2015, online edition of the journal *Nature Medicine* revealed that recipients of the single cell suspension transplant exhibited marked improvement in lung compliance. The treatment induced marked long-term lung chimerism with donor type structures or "patches" that contained epithelial, mesenchymal, and endothelial cells.

"Certain stem cells that normally reside in the lungs are highly similar to those in the bone marrow," said senior author Dr. Yair Reisner, professor of immunology at the Weizmann Institute of Science. "In each organ, the stem cells, rather than being distributed throughout the tissue, are concentrated in special compartments that contain all the provisions that stem cells need. That understanding suggested to us that we might be able to apply our knowledge of techniques for transplanting bone marrow stem cells to repairing lung tissue, but our real vision, bolstered by this success, is to create a bank of lung tissue that will be a resource for embryonic lung stem cells."

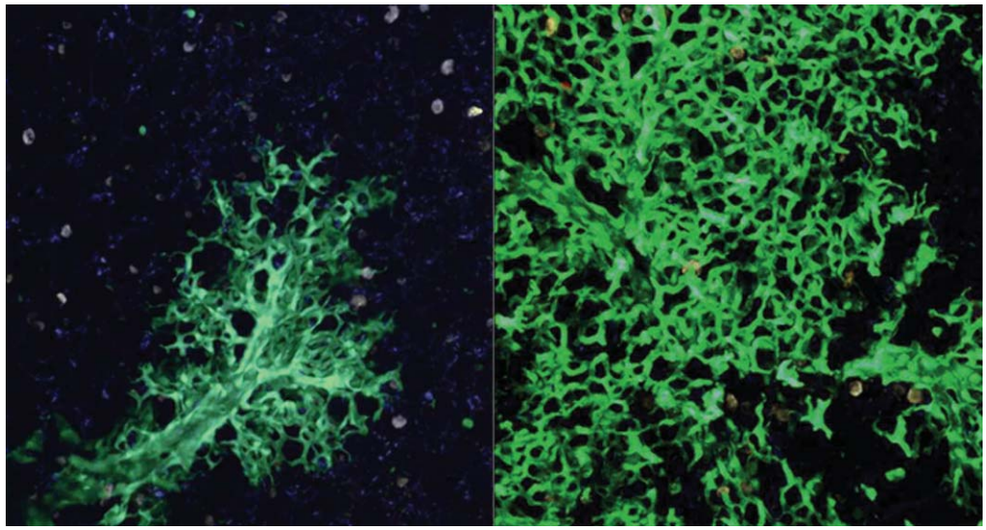


Image: New lung cells are continuously created to replace the damaged ones: Lung tissue six weeks after stem cell transplantation (left) and 16 weeks after transplantation (right). Cells that originated in the transplanted stem cells are green, as opposed to the uncolored host lung cells (Photo courtesy of the Weizmann Institute of Science).

Collaboration to Automate Sample Extraction Procedures

A collaborative agreement in the field of analytical chemistry will bring sample extraction of samples for chromatography directly to a series of automated, robotic liquid handling platforms.

The agreement will see the adaptation of the Phenomenex, Inc. (Torrance, CA, USA; www.phenomenex.com) Strata and Strata-X SPE solid phase extraction (SPE) tools for use on the Tecan (Männedorf, Switzerland; www.tecan.com) Freedom EVO series of robotics workstations.

SPE is a widely used technique for preparing samples prior to chromatographic analysis. Phenomenex Strata and Strata-X SPE sorbents remove unwanted contaminants, including phospholipids, and are offered with a number of discrete specificities that cover a diverse range of analytes.

The Tecan Freedom EVO series offers worktables with building-block modularity that ensures precision, reliable liquid handling, and easy-to-use robotics. Each platform can be combined with a wide choice of robotic arms, liquid handling tools, and application options powered by straightforward software that can be programmed to meet the needs of each individual laboratory. The EVO platform allows a choice of pipetting technologies on the same platform, including the possibility of combining both air and liquid displacement on a single workstation.

The two companies will jointly market Phenomenx SPE reagents that have been adapted for use on the Tecan Freedom EVO. Tecan will provide the instruments and automation support, and Phenomenex will provide the extraction chemistries as well as application and method development. The modified instruments will be particularly suitable for high-throughput customers in pharmaceutical research, clinical, and food testing environments using mass spectrometry detection methods.

"We created this agreement with our high-throughput customers in mind," said Michael McGinley, core products manager at Phenomenex. "We can now bring them complete, automated solutions, simplifying the previously daunting task of adapting a manual method to laboratory automation. The engineers at Tecan have an amazing insight on how to optimally automate liquid handling and the Freedom EVO is a proven platform with an established track record for reliability."

Image: The Evo Freedom workstation (Photo courtesy of Tecan).

"Phenomenex has a large customer base using their SPE products," said James O'Brien, head of clinical diagnostics at Tecan. "By co-marketing our robotic workstations with their chemistries, we expect to expand our reach in these high-volume industries."

Newly-Identified DNA Enables Growth of Wild-Type Hepatitis C Virus in Cell Cultures

A team of molecular virologists has found that the overexpression of a particular DNA in liver cancer cells enables these cells to maintain the growth of wild-type *Hepatitis C virus* (HCV) in culture.

Since its discovery in 1989, efforts to grow clinical isolates of HCV in cell culture have met with limited success. Only the JFH-1 isolate has the capacity to replicate efficiently in cultured liver cells without first undergoing cell culture-adaptive mutations.

Investigators at The Rockefeller University (New York, NY, USA; www.rockefeller.edu) hypothesized that cultured cells lack one or more factors required for the replication of clinical isolates. To identify these factors, the investigators used a pooled *Lentivirus*-based human complementary DNA (cDNA) library to transfect cultures of liver cancer cells with HCV subgenomic replicons lacking any adaptive mutations, and then selected for stable replicon colonies.

Results from screening more than 7,000 human genes by this process were published in the August 12, 2015, online edition of the journal *Nature*. They revealed the identification of a single cDNA, SEC14L2, which enabled RNA replication of diverse HCV genotypes in several liver cancer cell lines. This effect was dose-dependent and required the continuous presence of SEC14L2.

Remarkably, SEC14L2-expressing liver cancer cells also supported HCV replication following inoculation with patient sera. Mechanistic studies suggested, and the investigators speculated, that SEC14L2 promoted HCV infection by enhancing vitamin E-mediated protection against lipid peroxidation.

"Being able to easily culture HCV in the lab has many important implications for basic science research," said senior author Dr. Charles M. Rice, professor of virology at The Rockefeller University. "There is still much we do not understand about how the virus operates, and how it interacts with liver cells and the immune system."

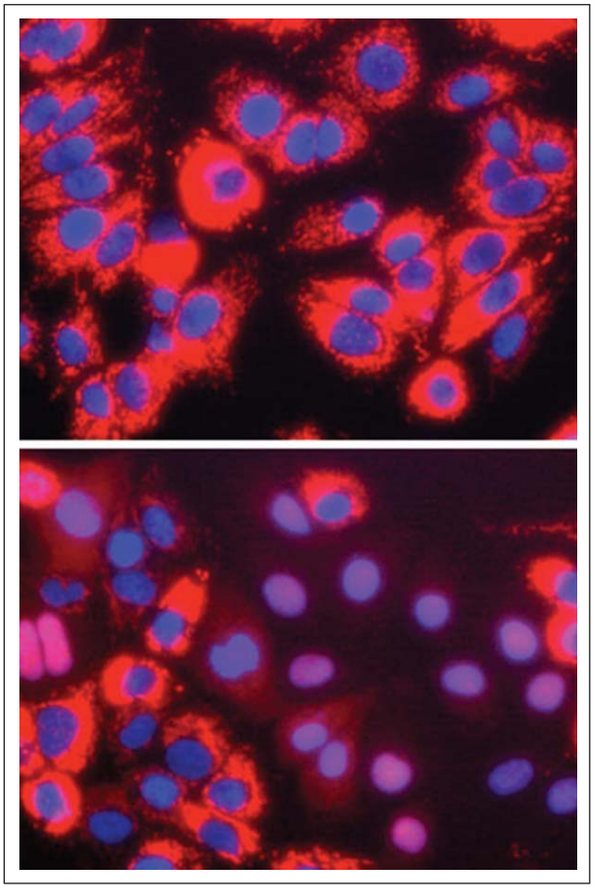


Image: Researchers engineered cultured cells to contain a red marker that moves into the nucleus upon HCV infection. Nothing happened when normal cells were exposed to HCV (top), but when the researchers expressed the protein SEC14L2, some nuclei changed color from blue to purple (bottom) (Photo courtesy of Laboratory of Virology and Infectious Disease at The Rockefeller University).

Bristol Myers Acquisition to Boost Development Of Nitroxyl-Based Cardiovascular Drugs

A major international biopharmaceutical company has announced the acquisition of a private biotech company that specializes in the development of drugs for treatment of cardiovascular disease.

Bristol-Myers Squibb Co. (New York, NY, USA; www.bms.com) has initiated the process to buy Cardioxyl Pharmaceuticals Inc. (Chapel Hill, NC, USA; www.cardioxyl.com).

Bristol-Myers Squibb is a global biopharmaceutical company dedicated to the discovery, development, and delivery of innovative medicines to patients with serious diseases. The company's operational strategy combines the reach and resources of a major pharmaceutical company with the entrepreneurial spirit and agility of a successful biotech company. This allows it to focus on customers' needs, giving maximum priority to accelerating pipeline development, delivering sales growth, and continuing to manage costs.

Cardioxyl Pharmaceuticals is a privately held, clinical stage biopharmaceutical company developing therapies for the treatment of cardiovascular disease, focusing on the discovery, development, and commercialization of novel technologies for disease areas where current therapies do not exist, are ineffective, or are inadequate.

Germany's Merck to Collaborate with Polish Concern on Cancer Drug Development

Two European-based biopharmaceutical companies have agreed to collaborate on the development of new anticancer therapeutic agents. The venerable – founded in 1668 – pharmaceutical and chemical company Merck (Darmstadt, Germany; www.merck.com) has entered into a three-year collaborative agreement with Selvita (Krakow, Poland; www.selvita.com), which has been in the drug development business since 2007.

The objective is to identify and exploit potential first-in-class small molecules as lead candidate drugs for multiple types of cancer. Each partner will contribute funding and resources to support the collaboration, as well as bring their expertise in target validation, bioinformatics, medicinal chemistry, in vitro and in vivo biology, and toxicology.

Under the terms of the agreement, Merck will have an exclusive license to any joint intellectual property, and Selvita will receive milestone payments and royalties upon Merck's successful completion of product development and commercialization. The project includes a joint research phase up to lead identification, after which Merck will continue to develop any candidate drug.

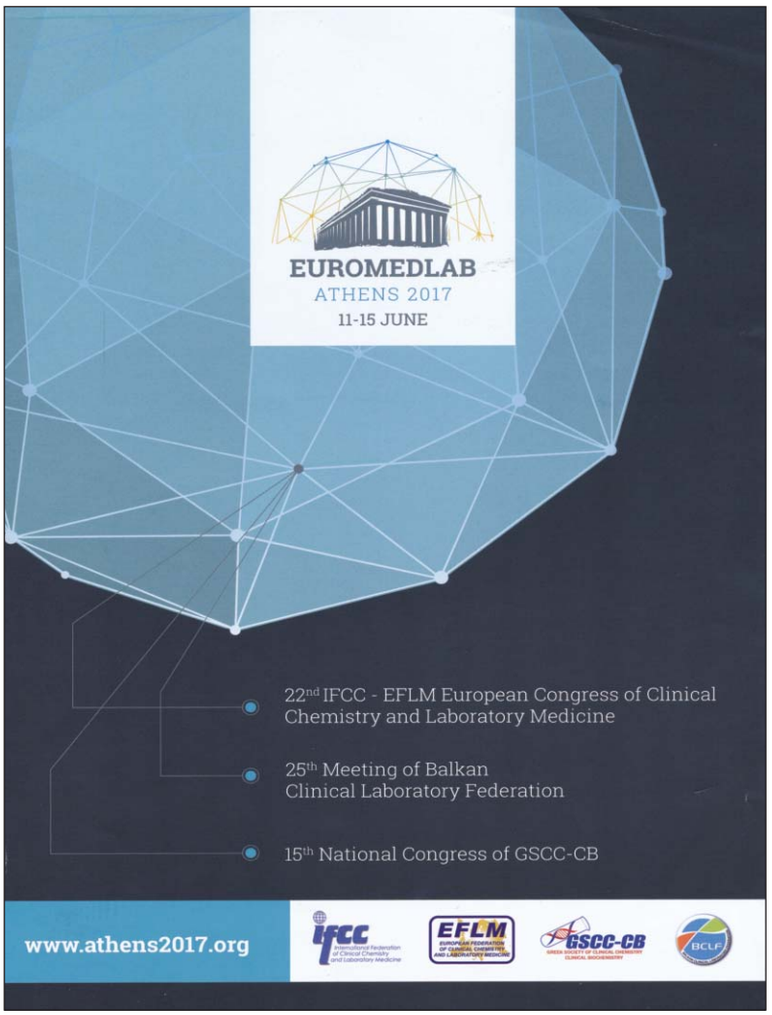
J&J Affiliate in Research Alliance with Danish Group on Low Molecular Weight Drugs

A collaborative agreement between American and Danish biopharmaceutical companies is expected to advance the discovery of new low molecular weight drugs.

Nuevolution A/S (Copenhagen, Denmark; www.nuevolution.com) has announced that it has entered into a collaborative agreement with Janssen Biotech, Inc. (Horsham, PA, USA; www.janssenbiotech.com). Janssen is a subsidiary of the international medical device, pharmaceutical, and consumer packaged goods manufacturer Johnson & Johnson (New Brunswick, NJ, USA; www.jnj.com).

The collaboration is intended to generate new low molecular weight drugs by exploiting Nuevolution's proprietary Chemetics drug discovery platform. Chemetics is a unique, patent protected drug discovery platform for both identification and optimization of hit to drug candidates. It is a hybrid of proven wet chemistry and molecular biology that enables DNA encoded synthesis of billions of chemically diverse drug-like small molecule compounds, and the efficient screening and optimization of these, facilitating effective identification of drug candidates at an unprecedented speed and scale.

Within the framework of the collaboration, Nuevolution will apply its Chemetics platform to discover and advance drug candidates against drug targets of interest to Janssen. Under the terms of the agreement, Nuevolution will receive an upfront payment, research funding, and would be eligible to milestone payments upon achievement of specified research, development, and commercial milestones.



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MedLab Middle East. Jan 25-28; Dubai, UAE; Web: www.medlabme.com

▶ February 2016

Stem Cell Models of Neural Degeneration and Disease. Feb 1-3; Dresden, Germany; Web: www.isscr.org

Biosimilar Drug Development World Europe 2016. Feb 10-11; Barcelona, Spain; Web: www.terrapinn.com

ACMR 2016 - 3rd Annual International Conference on Advances in Cancer Medical Research. Feb 22-23; Singapore, Singapore; Web: www.cancerresearch-conf.org

Cell Culture World Congress 2016. Feb 23-24; Munich, Germany; Web: www.terrapinn.com

11th Annual Biomarkers Congress. Feb 25-26; Manchester, UK; Web: www.biomarkers-congress.com

Biophysical Society Annual Meeting 2016. Feb 27-Mar 7; Los Angeles, CA, USA; Web: www.biophysics.org

▶ March 2016

Annual Meeting of the American Academy of Allergy, Asthma and Immunology. Mar 4-7; Los Angeles, CA, USA; Web: http://annualmeeting.aaaai.org

CHI 2016 – 23rd International Molecular Medicine Tri-Conference. Mar 6-11; San Francisco, CA, USA; Web: www.triconference.com

PITTCON 2016 – Pittsburgh Conference on Analytical Chemistry and Applied Spectroscopy. Mar 6-10; Atlanta, GA, USA; Web: http://pittcon.org

11th European Molecular Imaging Meeting. Mar 8-10; Utrecht, Netherlands; Web: www.emim.eu

Lab-on-a-Chip Europe 2016. Mar 14-14; Madrid, Spain; Web: http://selectbiosciences.com

Biotech World 2016. Mar 15-17; Moscow, Russia; Web: www.mosbiotechworld.ru

ARABLAB 2016. Mar 20-23; Dubai, UAE; Web: www.arablab.com

Society for General Microbiology Annual Conference 2016. Mar 21-24; Liverpool, UK; Web: www.sgm.ac.uk

Neurological Biomarkers Conference. Mar 21-23; San Diego, CA, USA, United States; Web: www.gtcbio.com

Drug Discovery Technology World Asia. Mar 22-24; Singapore; Web: www.terrapinn.com

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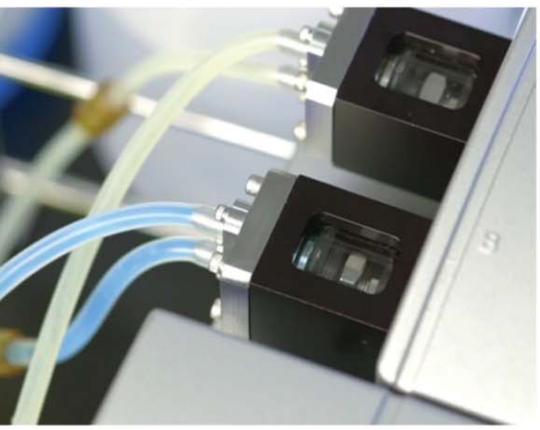

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