

EUROPE

Biomarkers for Autism Discovered

An important step towards developing a rapid, inexpensive diagnostic method for autism has been taken by Uppsala University, in collaboration with other universities. Through advanced mass spectrometry the researchers managed to capture promising biomarkers from a tiny blood sample. The study has just been published in the prestigious journal *Nature Translational Psychiatry*.

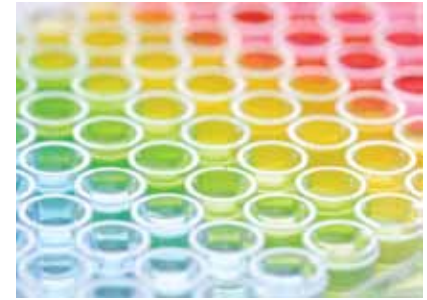
There are no acknowledged biomarkers for autism today. Researchers at Berzelii Centre and the Science for Life Laboratory in Uppsala who, in collaboration with colleagues at Linnaeus University in Sweden and the Faculty of Medicine in Tehran, Iran, who have discovered some promising biomarkers.

Many diseases are caused by protein alterations inside and outside the body's cells. By studying protein patterns in tissue and body fluids, these alterations

can be mapped to provide important information about underlying causes of disease. Sometimes protein patterns can also be used as biomarkers to enable diagnosis or as a prognosticating tool to monitor the development of a disease. In the current study disruptions of the nervous system were in focus when the scientists studied protein patterns in autism spectrum disorder (ASD).

To identify potential biomarkers (peptides or proteins), the researchers performed a detailed protein analysis of blood plasma from children with ASD compared with a control group. Using advanced mass spectrometric methods, they succeeded in identifying peptides consisting of fragments of a protein whose natural function is in the immune system, the complement factor C3 protein.

The study is based on blood samples from a relatively limited group of children,



but the results indicate the potential of our methodological strategy. There is already a known connection between this protein and ASD, which further reinforces the findings, says Jonas Bergquist, professor of analytical chemistry and neurochemistry at the Department of Chemistry – BMC (Biomedical Centre) in Uppsala.

The hope is that this new set of biomarkers ultimately will lead to a reliable blood-based diagnostic tool.

New Research Could Stop Tumor Cells From Spreading

Researchers from the Department of Chemistry and Molecular Biology at the University of Gothenburg have managed for the first time to obtain detailed information about the role of the protein metastasin in the spread of tumour cells.

Published recently in the renowned *Proceedings of the National Academy of Sciences (PNAS)*, the study paves the way for the development of new drugs. Metastasin is a protein with a key role in the spread of tumour cells. Previous research has shown that it is activated through the binding of calcium ions and then binds to and modulates other proteins.

One of metastasin's binding partners is a motor protein called non-muscle myosin. Motor proteins are the driving force behind

cell mobility. By binding to this protein, metastasin can increase the spread of tumour cells, acting as a kind of gas pedal for the cancer engine.

"Using a method called X-ray crystallography, we have managed for the first time to obtain detailed information on how metastasin binds to a motor protein, a process that facilitates the spread of tumour cells", explains researcher Gergely Katona.

It has been possible to image metastasin and calcium-ion-bound metastasin using X-ray crystallography before, but the researchers at the University of Gothenburg are the first to have imaged the structure of calcium-ion-activated metastasin with an attached non-muscle myosin fragment.

"This has given us information about

regions of both metastasin and the motor protein that are crucial for metastasin's ability to bind to the motor protein. This is important to know for drugs to be developed that block these specific regions and so prevent this binding...The image of the two molecules gives us a better understanding of how metastasin binds to the motor protein, so increasing cell mobility and the spread of tumour cells. This understanding in turn paves the way for the development of new drugs to prevent this harmful interaction between molecules and so stop tumour cells from spreading."

The metastasin and the motor protein can be imaged as a snapshot, but the next stage is to create a kind of video to see how the molecules move when binding to one another.

Dutch Scientists Deliver Drugs with Nanorockets

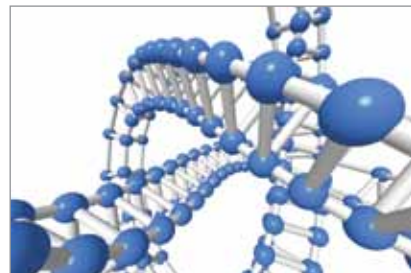
Dutch scientists have successfully launched nanosized rockets that they envision eventually carrying drugs through the body to a vital target.

A team of researchers at Radboud University Nijmegen in The Netherlands led by Jan van Hest, built nanoparticles about 10 times smaller than a bacteria that assemble into tiny orbs, fueled by hydrogen peroxide. To build the nanorockets, they started with ball-shaped containers known as polymersomes. Next, they incorporated other molecules into the construction and then

linked them to functional enzymes. Peptides are on the outside. Platinum nanoparticles decompose the fuel into oxygen and water, which sends the vessel thrusting in a given direction.

While the concept does look tantalizingly futuristic, researchers admit the technique has a long way to go. For one, the hydrogen peroxide fuel is toxic in humans. An alternative non-toxic fuel would improve the method considerably, but even this would face the problem any rocket faces – refueling. Steering and controlling these

nanorockets amidst the mass of complex tissues is another problem that Jan's team is likely to tackle. Details of the study are published in *Nature Chemistry*.



"Living" Micro-Robot Could Detect Diseases in Future

A tiny prototype robot that functions like a living creature is being developed which one day could be safely used to pinpoint diseases within the human body. Called 'Cyberplasm', it will combine advanced microelectronics with latest research in biomimicry (technology inspired by nature). The aim is for Cyberplasm to have an electronic nervous system, 'eye' and 'nose' sensors derived from mammalian cells, as well as artificial muscles that use glucose as an energy source to propel it.

The intention is to engineer and integrate robot components that respond to light and chemicals in the same way as biological systems. This is a completely innovative way of pushing robotics forward.

Cyberplasm is being developed over the next few years as part of an international collaboration funded by the Engineering and

Physical Sciences Research Council (EPSRC) in the UK and the National Science Foundation (NSF) in the USA. The UK-based work is taking place at Newcastle University. The project originated from a 'sandpit' (idea gathering session) on synthetic biology jointly funded by the two organisations.

Cyberplasm will be designed to mimic key functions of the sea lamprey, a creature found mainly in the Atlantic Ocean. It is believed this approach will enable the micro-robot to be extremely sensitive and responsive to the environment it is put into. Future uses could include the ability to swim unobtrusively through the human body to detect a whole range of diseases.

The sea lamprey has a very primitive nervous system, making it easier to mimic than more sophisticated nervous systems. This, together with the fact that it swims, made the sea lamprey the best candidate for the project team to base Cyberplasm on.

Once it is developed the Cyberplasm prototype will be less than 1cm long. Future versions could potentially be less than 1mm long or even built on a nanoscale. "Nothing matches a living creature's natural ability to see and smell its environment and therefore to collect data on what's going on around it," says bioengineer Dr Daniel Frankel of Newcastle University, who is leading the UK-

based work.

Cyberplasm's sensors are being developed to respond to external stimuli by converting them into electronic impulses that are sent to an electronic 'brain' equipped with sophisticated microchips. This brain will then send electronic messages to artificial muscles telling them how to contract and relax, enabling the robot to navigate its way safely using an undulating motion.

Similarly, data on the chemical make-up of the robot's surroundings can be collected and stored via these systems for later recovery by the robot's operators. Cyberplasm could also represent the first step on the road to important advances in, for example, advanced prosthetics where living muscle tissue might be engineered to contract and relax in response to stimulation from light waves or electronic signals. "We're currently developing and testing Cyberplasm's individual components," says Daniel Frankel. "We hope to get to the assembly stage within a couple of years. We believe Cyberplasm could start being used in real-world situations within five years".

For more information on the synthetic biology sandpit that led to this collaboration between EPSRC and NSF visit: <http://www.epsrc.ac.uk/newsevents/news/2009/Pages/syntheticbiologyandsandpit.aspx>



Animal Import Bans Threaten UK Drug Research

Vital medical research is under threat in Britain because ferry companies and airlines are bowing to pressure from animal rights activists and refusing to carry animals destined for laboratory testing, scientists and drugmakers said early in March.

All ferry companies operating routes into Britain have now banned the import of mice, rats and rabbits, which are used in research labs to explore the potential of experimental new drugs.

"Threats to the carriage of these animals will slow down the progress of essential and life-saving biomedical research," scientists from the Medical Research Council, the Association of the British Pharmaceutical Industry, the Association of Medical Research Charities and others said. While the vast majority of animals used for research in Britain are bred here, there are certain programmes where experts from different parts of the world find it essential to share specific strains of animals, scientists said.

"It takes a long time to breed these animals, and if their transport is stopped then researchers will have to recreate them, requiring the unnecessary use of many more animals over successive generations," they said in a joint statement. With strict rules in place to ensure humane transport, international animal transit mostly relies on airlines, partly because flying means shorter travel times.

In Britain, however, ferries have been increasingly relied upon since previous campaigns by animal rights activists prompted airlines and airports to withdraw from the business. But in recent months ferry companies that serve Britain, including DFDS and P&O Ferries, have also stopped carrying laboratory animals. Michelle Ulyatt, a spokeswoman for P&O Ferries, said its decision to halt live animal imports was

taken last year "under sustained pressure from anti-vivisection groups".

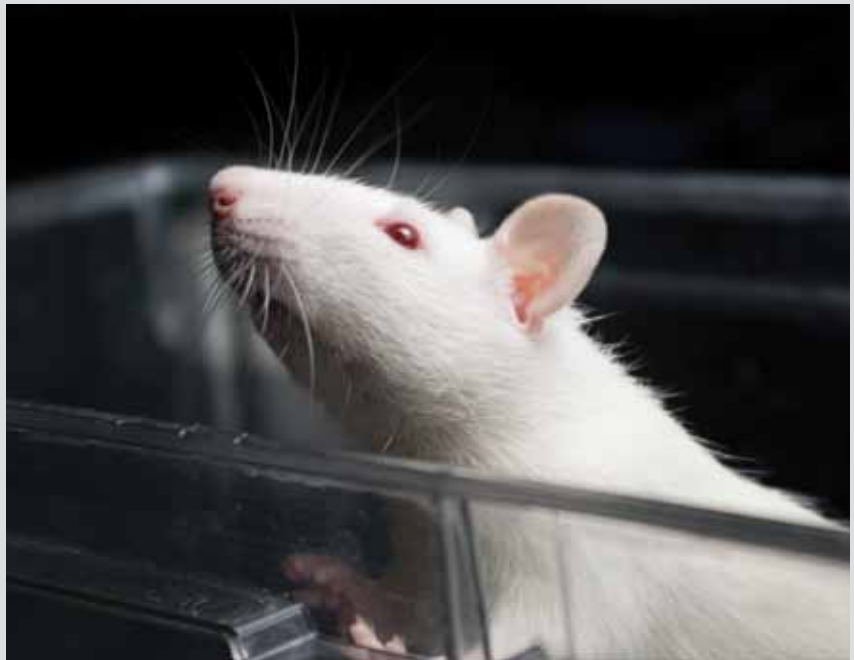
"Our primary concern is ensuring staff safety and our corporate reputation," she told Reuters, adding that at the height of campaigns against ferry companies, letter bombs had been sent to transport executives. The stand-off over importing animals for research poses a dilemma for Prime Minister David Cameron, who has said he is determined to make Britain a prime location for scientific investment, particularly in the pharmaceutical sector.

"We're going to be more flexible, more competitive, more hungry for your business than ever before," he told executives at a recent global pharma and biotech conference in London. Britain has been particularly reliant on pharmaceutical firms for success in manufacturing and is home to two of the world's top drug companies in GlaxoSmithKline and AstraZeneca. But the

industry has been under pressure in recent years and forced to make cuts.

Cameron has said Britain is feeling the fall-out of the global challenges now facing the sector, with the world's No. 1 pharma firm Pfizer closing a research and development site in Sandwich, southern England, and AstraZeneca pulling out of its Charnwood research site in central England. Responding to the scientists' statement, science minister David Willetts said it was a "serious problem" the government was determined to tackle.

"We are trying to hammer out a deal in which both the life sciences industry agree a kind of code of conduct on exactly how animals ... will be transported, and in return the transport industry ... would all agree that they would continue to transport animals," he told BBC radio. "That's what we still hope we can put together. It makes sense for everyone."



£100M Welsh Biotech Fund Inspired by Sir Chris Evans

The high-profile biotech investor Sir Chris Evans has inspired the Welsh government to commit £50 million to a new life sciences fund, which will look for matching cash to double the size of the effort. And Evans believes he can rope in private investors willing to contribute £200 million to the cause, potentially setting up an operation with more than \$375 million.

Wales is starting out with £25 million now with plans to chip in another £25 million next year. Their goal is to create a biotech hub that can attract venture cash from outside the region and spin out new companies, creating an engine for economic growth. And Evans sees a day when the fund can earn back more money that can continue to be invested in the field.

"We will be looking at doing packages of investment between £500,000 and £10 million in any one company," Sir Chris told a biotech crowd in Wales, according to a report in WalesOnline. "Where it's the bigger number, say £5 million, we would expect some of that to be co-investment which we would bring in from elsewhere in the UK and elsewhere."

Sir Chris is no stranger to big plans. He runs the Merlin venture funds at the Excalibur group and he's been spotlighted as a key figure behind the shadowy NCPharma, which has reportedly gathered substantial backing to launch a major new drug development effort. A year ago he was brought in by the Welsh government to advise officials on biotech policy. He evidently arrived with some ambitious plans.

The news put Wales' biotech industry squarely in the spotlight, a rare occasion for the group. Most of the attention for the country's R&D industry has been centered around Cambridge and in London, where government officials have been working on their own biotech support programs.



Scientists Discover New Plasmodium Mechanism

Genome Research has just published the results of a study led by researchers at the Barcelona Centre for International Health Research (CRESB) revealing a hitherto unknown mechanism that enables the malaria parasite *Plasmodium falciparum* to adapt to common fluctuations in its environment. A substantial part of the research was also carried out at the Institute for Research in Biomedicine (IRB Barcelona) and the Nanyang Technological University (Singapore).

The authors of the article have shown how, in a genetically homogeneous population of *P falciparum* parasites, each parasite is different. Using new highly accurate methods of analysis, the scientists discovered that more than 5% of the genes expressed in some parasites are repressed or silenced in other, genetically identical, parasites. Depending on which genes it uses or expresses, each parasite will be able to adapt to specific changes in its environment.

This means that, in any population of *P falciparum*, some parasites are spontaneously pre-adapted to the fluctuations commonly found in their environment, such as changes in the immune or metabolic conditions of the human host (eg malnutrition), the episodes of fever typical of malaria, the presence of antimalarial drugs, and the presence or absence of competition from other parasites. The mechanisms that mediate this spontaneous adaptation are epigenetic.

INDIA

Landmark Gleevec IP Case Makes Big Pharma Think Twice

Why should we push into emerging markets where intellectual property may not be safe? That's the question pharma giants—and now U.S. officials—are asking, as India's top court mulls over a landmark patent case involving Novartis' Gleevec. The Indian government previously ordered that Bayer (\$BAY) allow domestic drugmaker Natco Pharma to knock off its cancer drug Nexavar at a vastly reduced price.

The two cases are making pharmaceutical companies sit up, as their profit margins are being threatened. If innovative drugs are not protected, then how can the makers of those drugs profit? At the same time, if drug developers are not willing to lower the price of their drugs in developing countries whose citizens can barely afford to pay for food, much less medication, then why enter these markets in the first place? What good is a lifesaving drug if only a tiny fraction of patients have access to it?

Still, Big Pharma is not giving up without a fight. U.S. Commerce Secretary

John Bryson has told Indian Commerce Minister Anand Sharma, that "(a)ny dilution of the international patent regime was a cause for deep concern for the U.S.," a government official said. Sharma countered, saying the World Health Organization's compulsory licensing provisions were established for cases just like this—life-threatening illness treated by a drug out of reach at brand-name prices.

If brand-name pricing is indeed still being practiced in emerging markets, then it calls Big Pharmas' strategy into question. One usually expects companies to reduce prices considerably in order to take advantage of India's burgeoning middle class. The sheer volume of this demand ought to assuage any concerns of a drop in price, so why keep the drugs at exorbitant prices, knowing fully well the consumer base will be severely restricted? Could companies like Bayer and Novartis be regretting their venture into the sub-continent now that market exclusivity of their drugs is no longer guaranteed?



The stakes are high because should Novartis succeed in striking down the Indian patent provision in question, a slew of other patent cases could open up, making many drugs suddenly inaccessible. Novartis maintains that access to medicines depends on patent protection. The company "is seeking clarity on whether we can rely on patents in India and whether we as a research-based organization can continue to invest in the development of better medicines for India," Novartis' top official in India, Ranjit Shahani, said.

Indian Govt Defends Generics Industry

Indian Commerce Minister Anand Sharma is blasting what he says are attempts to smear the country's generic drug industry as substandard or inferior. As reported in The Economic Times, the minister is also seeking support from African countries to back the industry and its effort to bring affordable treatments to poor people in both regions.

"There is a campaign to showcase generics as substandard, that they are not real," Indian Commerce Minister Anand Sharma said in the The Economic Times article. "We are determined to ensure that poor people in my country and in Africa have access to these medicines."

Sharma, speaking at the 8th annual India-Africa Project Partnership Summit, was referring to The U.S. Department of Justice

earlier this year negotiating a substantial settlement with Indian generic drugmaker Ranbaxy Laboratories over everything from false data to quality-control problems at both U.S. and Indian plants, as well as a



scathing "Dateline NBC" report suggesting ethics problems at two Indian CROs.

India has aggressively pursued development of cheaper, generic medicines for its population. Those generic drugs treat cancer, AIDS and other major diseases, and have brought down the cost of medicines in a major way, Sharma said. Recently, the government for the first time invoked its compulsory licensing rules, allowing domestic drugmaker Natco Pharma to make and sell a generic version of Bayer's cancer drug Nexavar, even though the drug is not on patent. Health.India.com notes that the generic price will be 97% cheaper, but argues that the drug is still unaffordable and should be added to a list of generics that public healthcare facilities can give for free.

JAPAN

Japan May Open \$96 Billion Drug Market Further

The Japanese government might allow seriously ill patients to use medical treatments not yet approved in Japan under a "compassionate use" system, in a move that signals the country is opening the door further to foreign pharmaceutical companies.

Japan has been traditionally slow to approve new treatments developed overseas for its \$96 billion drug market, the world's second largest, due in part to safety concerns. But the government has recently taken steps to speed up the approval process and gain access to better treatment as it seeks to cut healthcare costs for its rapidly ageing society, creating business opportunities for western drugmakers.

Japan is considering allowing the use of drugs and medical devices that have already been approved in places such as the United States and Europe and which are undergoing clinical trials in Japan, said Toshio Miyata, assistant director at the licensing division of the Pharmaceutical and Food Safety Bureau.

The compassionate use programme, similar to ones already in place in western countries, would be for patients with advanced diseases that have not responded to standard treatments and where other domestic options are not available. Miyata said that the government hopes to submit legislation to parliament as early as this year, although no timeframe had been set and many details needed to be worked out.

Time would be needed to prepare regulatory approvals and insurance coverage under Japan's universal healthcare system. The Nikkei newspaper reported that the government may allow health insurance to pay for some of the costs patients might incur under the "compassionate use" system. But Miyata said nothing had been decided. In Japan, patients normally foot the bill themselves for non-approved treatments.

The Nikkei cited cancer drugs Zanosar, a tumor fighter made by privately held French firm Keocyt, and Firmagon, a hormonal therapy for advanced prostate cancer made by unlisted Switzerland-based

Ferring Pharmaceuticals, as examples of treatments available abroad that have not yet been approved in Japan. Miyata would not discuss specific drugs.

Western drugmakers are seeking to expand their presence in Japan, considered an increasingly important country with its large middle-class and ageing population and better profit margins than those seen in emerging markets. Last year, Merck & Co, AstraZeneca Plc and GlaxoSmithKline Plc each won approval to sell some of their drugs in Japan. Britain's Glaxo announced this month it would form a 50-50 joint venture with Daiichi Sankyo to bring new vaccines to Japan, targeting an underdeveloped segment of the overall market.

Japan's government also aims for generic drugs to make up 30 percent of the market by the fiscal year ending in March 2013 from about 20 percent in 2010, prompting the likes of Pfizer Inc and Israel's Teva Pharmaceutical Industries to enter the market.



SINGAPORE

Temasek Foundation and Temasek Life Sciences Laboratory Collaborate in Myanmar

Temasek Life Sciences Laboratory (TLL) and Temasek Foundation (TF) have announced the commencement of a technical co-operation in partnership with Myanmar's National Health Laboratory to develop capabilities in the area of laboratory biorisk management of emerging infectious diseases. The programme will be funded by a grant of S\$200,000 from TF.

An initial group of 25 participants have been selected by their respective agencies to participate in the first phase of a series of training programmes. They will pass on the knowledge and experience to their peers and other technical staff in Myanmar after the training has been completed. The establishment of these training programmes will help to build the foundation for future

partnerships between Singapore and Myanmar which will accelerate the use and deployment of technology and knowledge towards improving the level of biorisk security as well as preparedness against future emerging diseases in Myanmar.

Through this partnership, TF and TLL hope to develop nationwide and institutional capabilities and capacity building of professionals in Myanmar to manage laboratory biorisks in line with the global health programme of the World Health Organisation in Myanmar. Working closely with the National Health Laboratory in Myanmar, TLL has developed a customised programme that will be used for future training needs in Myanmar.

This programme follows the success of

the inaugural training programme in Laos in 2010 where TLL and TF collaborated with the National Emerging Infectious Diseases Coordination Office (NEIDCO), a national agency in Laos to develop nationwide and institutional capabilities in laboratory biorisk management. Laboratory professionals were similarly trained in managing biorisks and have started to share their learning with other key hospitals and laboratories in Laos. TF and TLL will continue to support similar biorisk management programmes in other ASEAN countries over a four-year period.

Since 2004, TLL has carried out various biorisk and biosafety training programmes with governmental agencies from various regional countries and will adapt from the experiences of working with these agencies.



NCIS, NCCS and ESMO to Launch Cancer Education Initiative

The European Society for Medical Oncology (ESMO), the National Cancer Centre Singapore (NCCS) and the National University Cancer Institute, Singapore (NCIS) recently announced the launch of a joint education initiative for cancer doctors in Singapore as the incidence of colorectal cancer cases and deaths rapidly rises in both Singapore and in Asia.

The ESMO-Asia Continuing Medical Education (CME) Program for Colorectal Cancer sees the establishment of a new, world-class medical education platform between ESMO and 35 regional cancer centres and hospitals, giving cancer doctors access to the latest scientific knowledge and information on patient-centric care strategies. A long-term education initiative, the programme will offer a unique "East-meets-West" platform for knowledge sharing and collaborations among oncology professionals from both Europe and Asia, with the aim of improving care for colorectal cancer patients at every stage of their treatment journey. Through this program, ESMO intends to fulfill its goal to promote knowledge sharing and enhance professional development of oncology practitioners, who will in turn provide effective treatment and high-quality care for cancer patients.

Partner centres NCCS and NCIS will be responsible for conducting local meetings for fellow institutions and/or surrounding hospitals, promoting further collaborations between Asian and Western oncologists to maintain the high standard of qualifications of all medical professionals for the optimal management of colorectal cancer. The program is launched with a view that long-term adaptation of the comprehensive East-West program for Asian medical oncologists will lead to standardised clinical protocols and treatment goals based on the best practice approach.

"It is truly a privilege for us at NCCS to partner the European Society of Medical Oncology to establish this colorectal cancer continuing medical education initiative in Singapore. The ESMO-Asia CME Program will further educate, enable and empower

cancer specialists towards best practices to provide best care to colorectal cancer patients. Indeed research and clinical advances in cancer progress so fast that such an enterprise is all the more timely," said Dr Toh Han Chong, Head of Department of Medical Oncology, NCCS.

Echoing the sentiment, Dr Robert Lim, Associate Director (Clinical), NCIS, said: "Colorectal cancer is a common problem affecting both Western and Asian countries. This opportunity to share cutting-edge knowledge and experience enables us to provide the best management strategies for all our patients. In particular, complex cases that require inter-disciplinary care and discussion will benefit significantly from these interactions."

More than one million cases of colorectal cancer are diagnosed worldwide every year and around half of those diagnosed will die of their disease. A reason for the poor outlook is because one in every four patients only seeks treatment after their disease has spread to other parts of the body, reducing their chances of cure.

In Singapore, colorectal cancer is the second most common cause of cancer deaths among men and the third most common cause among women. In terms of occurrence, it has taken over lung cancer in the last five years to become the most frequently occurring cancer among Singapore males and is the second most recurring cancer after breast cancer for females.

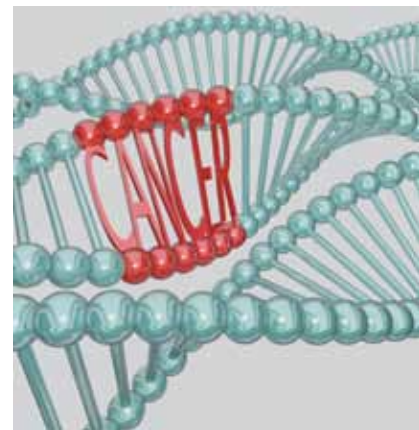
Recent research demonstrates that personalised treatment for colorectal cancer by identification of specific molecules (also called 'biomarkers') can help physicians identify which patients are most likely to benefit from a specific treatment. This breakthrough enables oncologists to select the most appropriate treatment for patients from the point of diagnosis and thus improves their overall long-term outcomes.

The ESMO-Asia education initiative is unique because it brings together all of the medical experts involved in treating the patient and draws upon their specific experience at each stage in the delivery of

treatment. This multi-disciplinary approach is part of a broader move to develop more patient-centric treatment strategies in order to improve both the patient's quality of care and quality of life. In 2012, ESMO-Asia plans to establish further educational platforms across the region with a localised curriculum for each country, creating well-designed, rich and challenging scientific programmes as well as opportunities to share updates on colorectal cancer management.

The ESMO-Asia CME Program is sponsored in part by an unrestricted educational grant by Merck Serono, the pharmaceutical division of Merck KGaA, a global pharmaceutical and chemical company. By working together with ESMO and the local oncology centres, Merck Serono is committed to the research and development of treatment options, as well as bringing the highest standard of medical knowledge to Asia and establishing these centres as "Centres of Excellence".

"Moving forward with this program will not only ensure that doctors are consistently equipped with the most recent and best knowledge coupled with the right skills to help them manage the disease but this in turn will also contribute to a real positive difference to the lives of the patients and their families. Merck Serono is happy to be one of the sponsors to provide an unrestricted educational grant support to this educational initiative", said Mr. Tim Kneen, Regional Vice President of Merck Serono, Asia Pacific.

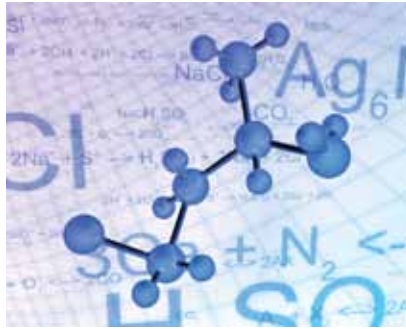


TAIWAN

Taiwan Lags Behind South Korea in Biotech

Early in March, Wong Chi-huey, president of Academia Sinica, the most prestigious academic institution in Taiwan, commented on Taiwan lagging behind South Korea in the development of its biotech industry. This is in addition to the lagging of its DRAM (dynamic random access memory) and FPD (flat panel display) industries.

Wong noted that the South Korean government aims to raise the nation's science R&D outlay to 5% of GDP, the highest in the world, compared with 4% in Japan and 2.9% in Taiwan. In addition, South Korea has proclaimed to become the world's seventh largest economy in several years. South Korea, has successfully commercialized four new medicines, including two developed



by LG Lifescience. In contrast, several Taiwanese biotech firms, such as Ptimer Biotechnology, Medigen Biotechnology, and TaiGen Biotechnology, are still stuck at the stage of clinical testing for their new drugs.

Samsung has established a dedicated biotech department and teamed up with

Quintiles Transnational and Biogen Idec — both of the U.S. — in developing biosimilar drugs last year. The two U.S. firms are original medicine developers but patents for their technologies are going to expire. Backed by the two U.S. firms, South Korea's Samsung will gain an edge over its Taiwanese competitors.

Still, it's not all doom and gloom for Taiwan, reiterated Wong. The country has achieved substantial progress in developing medicines for diseases common amongst Chinese people, such as antibody medicines for lung cancer and breast cancer. There is also a lot of untapped potential in mainland China, where developing drugs for the huge Chinese market could become very lucrative indeed.

NCHU Inaugurates Taiwan-U.S. Research Center on Plant and Food Biotech

National Chung-Hsing University (NCHU) in Taiwan and the University of California, Davis (UCD) in the U.S. have set up a research center on plant and food biotechnology in Taiwan under an NSC five-year, one hundred million NT dollars program to solicit abroad partnership. This was the first internationally cooperated center set up with the subsidy under the program since its beginning. With the center, an integration platform of the research resources and advantages of both sides could be provided.

The establishment of NCHU-UCD Plant and Food Biotechnology Center (PFBC) was directed by NCHU Professor Shyi-Dong YEH at the Department of Plant Pathology. The topics of the center was planned to cover plant development, Plant-pathogen interaction, functional food and cross-nation agriculture technology transfer. NCHU also planned to provide a research environment that is friendly to international scholars, expecting to solicit more globally top research talents.

As NCHU indicated, NCHU takes a leading position in the field of tropic and

subtropical agriculture research in the world, while UCD is the most important academic institute of agriculture sciences in the U.S., listed in the top 50 universities in the world during the past decade. Besides, UCD is also recognized as the topmost institute in the world in the fields of animal and plant sciences, agriculture and food technology.

The cooperation between the two universities is expected to enhance Taiwan's agriculture biotechnology and to lift Taiwan's academic impact and visibility in the globe. The research programs of the center are now divided in four core focuses, and six of them are integration plans. These programs will be executed by the researchers from the Department of Plant Sciences, Plant Pathology and Food Science and Technology, UCD and the Graduate Institute of Biotechnology, Department of Plant Pathology and Food Science and Biotechnology, NCHU.

This term, 18 research center establishment plans were submitted to the National Science Council (NSC), and four were approved. Besides the NCHU-UCD Plant and Food Biotechnology Center, a cross-national center on cancer among National

Taiwan University College of Medicine, China Medical University and The University of Texas MD Anderson Cancer Center; a cross-national center on intelligent robot among National Taiwan University, Université Pierre et Marie CURIE (France) and Institut National de Recherche en Informatique et en Automatique (France); and a center on super-computing between National Cheng Kung University and IBM Thomas J. Watson Research Center.



Taiwan Offers New Model to Predict Hepatitis C Cancer Risk

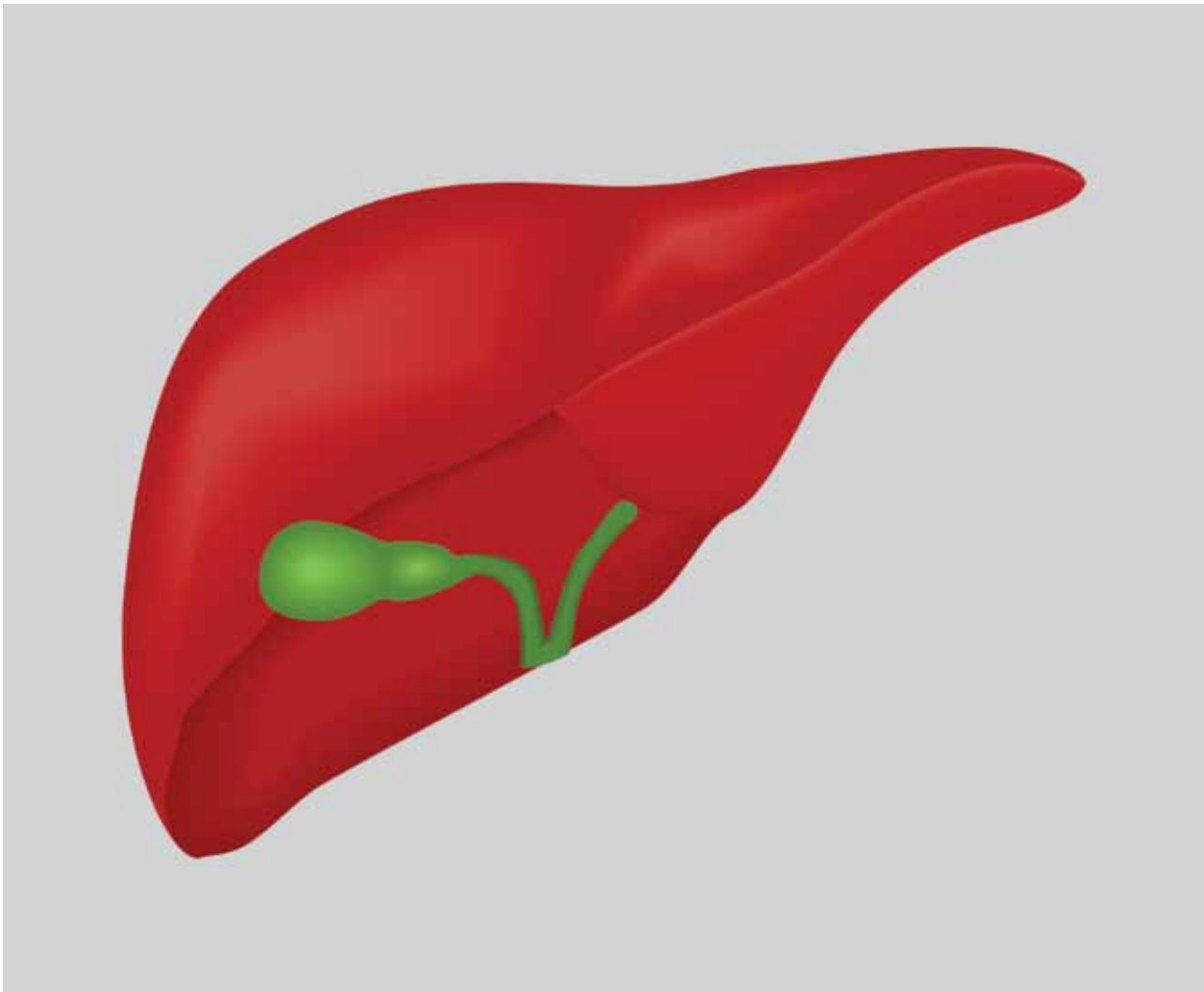
A Taiwan-led research team has successfully devised a new prediction model to calculate the likelihood of hepatitis C patients developing liver cancer, the team leader Chien-jen Chen, Vice President of Academia Sinica, said in February.

The model incorporates indicators such as age, the liver function indexes ALT and AST, hepatitis C virus RNA in

serum, cirrhosis and the genotype of the virus, said CHEN at a session of the Conference of the Asian Pacific Association for the Study of the Liver held in Taipei.

Chen said the serum data was particularly important in predicting the chances of developing liver cancer. The model, which can predict a result with 80 percent accuracy, assigns a score on 0-25

scale to analyze each case. The higher the score, the higher the risk of getting liver cancer, Chen said. Chen's team also launched a model in 2010 to calculate the chances of the hepatitis B virus developing into liver cancer. In future, the prediction models will be available on the Internet and in apps on smartphones to allow individuals to determine their own risk factor, Chen said.



Nobel Laureate Dr. Ada E. Yonath to Lecture in Taipei

Dr. Ada E. YONATH, one of the three 2009 Nobel Laureates in Chemistry, delivered two keynote speeches at Academia Sinica and National Taiwan University on March 6 and 7, respectively. The lectures were entitled "Is there a Limit to Life Expectancy? Wishes, Predictions and Reality" and "From Basic Research to Advanced Antibiotics".

Dr. YONATH is currently the Kimmel Professor of Structural Biology at the Weizmann Institute of Science and the Director of the Kimmelman Center for Biomolecular Structure and Assembly in Israel. In 2009, she received the Nobel Prize in Chemistry along with Dr. Venkatraman RAMAKRISHNAN and Dr. Thomas A. STEITZ for her studies on the structure and function of the ribosome, becoming the first Israeli woman to win the Nobel Prize out of ten Israeli Nobel laureates, the first woman from the Middle East to win a Nobel prize in the sciences, and the first woman to win the Nobel Prize for Chemistry since 1964.

Prof. YONATH is an Israeli crystallographer best known for her pioneer work on the structure of the ribosome. She uses X-ray crystallography supported by molecular biology, mutagenesis and biophysical methods to investigate protein biosynthesis. Over the last three decades, Professor YONATH has focused her research on the ribosome, the cellular particle translating the genetic code into proteins. She has looked at the origin of the ribosome and its inhibition by antibiotics. Professor YONATH deciphered the structure and mechanism of action of ribosomes.

Dr. YONATH focuses on the mechanisms underlying protein biosynthesis using ribosomal crystallography, a research line she pioneered over twenty years ago despite considerable skepticism from



the international scientific community. Ribosomes translate RNA into protein and because they have slightly different structures in microbes, when compared to eukaryotes, such as human cells, they are often a target for antibiotics. She determined the complete high-resolution structures of both ribosomal subunits and discovered within the otherwise asymmetric ribosome, the universal symmetrical region that provides the framework and navigates the process of polypeptide polymerization. Consequently she showed that the ribosome is a ribozyme that places its substrates in stereochemistry suitable for peptide bond formation and for substrate-mediated catalysis. Two decades ago she visualized the path taken by the nascent proteins, namely the ribosomal tunnel, and recently revealed the dynamics elements enabling its involvement in elongation arrest, gating, intra-cellular regulation and nascent chain trafficking into their folding space.

Her findings are crucial for developing advanced antibiotics. "These models are now used by scientists in order to develop new antibiotics, directly assisting the saving of lives and decreasing humanity's suffering," the Nobel Prize academy said.

The Academia Sinica Lecture series, lunched in 2009, is organized by President Chi-Huey WONG and sponsored by the Foundation for the Advancement of Outstanding Scholarship in an effort to build on the spirit of research and free exchange of scholarly knowledge. Invitation to speak as an Academia Sinica Lecturer is extended to top scholars from around the world and represents the highest lecture in Academia Sinica. Dr. Roger Yonchien TSIEN and Dr. Roger D. KORNBERG, respectively the Nobel Laureates in Chemistry in 2008 and 2006, and Dr. James D. WATSON who received the Nobel Prize for Physiology or Medicine in 1962, have been previous Academia Sinica Lecturers

USA

BIO Opens Nominations for 2012 Biotech Humanitarian Award

The Biotechnology Industry Organization (BIO) announced in March that it is accepting nominations for the fourth annual Biotech Humanitarian Award. As in years past, the Award will be given to an individual who has harnessed the potential of biotechnology to heal, fuel or feed the planet.

"The individuals behind the biggest ideas in biotechnology are discovering ground-breaking technologies to address some of the most complex health, environmental and sustainability challenges facing our world today" said BIO President and CEO Jim Greenwood. "The Biotech Humanitarian Award is our way of saying 'thank you' to the biotech innovators who are working on the frontlines to find cures for diseases and make people's lives and the life of our planet better every day."

The Humanitarian Award honors work that aims to reduce human suffering significantly, enhance the human experience in a way that has a clear and direct benefit

to society or improves the health of our planet. Additional consideration will be given to approaches that are at a turning point and may potentially have immeasurable influence.

Last year's Honoree was Dr. Paul Offit, a vaccine advocate who serves as the Chief of the Division of Infectious Diseases and the Director of the Vaccine Education Center at The Children's Hospital of Philadelphia. Dr. Offit was presented the Humanitarian Award in recognition of his 25 years spent dedicated to developing RotaTeq, one of the main vaccines currently used to fight rotavirus, a disease that is the leading cause of severe, dehydrating diarrhea in infants and young children.

The Award and a prize of \$10,000 will be presented at the 2012 BIO International Convention, in Boston, MA on June 18-21, 2012. Nominations are open to all individuals and can be accessed here. Nominees will be evaluated and judged on the following criteria: impact on future generations; impact

on contemporary society; contribution to the field of biotechnology; and level of innovation exhibited.

Qualified nominees for the Biotech Humanitarian Award will be professionals in the biotechnology field including scientists, researchers, academics, entrepreneurs, financiers, philanthropists, educators, advocates and others who have added value to society through their pursuit of biotechnology processes.

BIO represents more than 1,100 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products. BIO also produces the BIO International Convention, the world's largest gathering of the biotechnology industry, along with industry-leading investor and partnering meetings held around the world.



Pharmaceuticals Survey: Many Think Business Model Is Broken

Confirming pessimism about the state of the pharmaceutical industry, a recent survey of U.S.- and E.U.-based pharmaceutical sales and marketing executives reveals that 68 percent believe “the current business model is broken.” The survey, conducted jointly by Booz & Company and National Analysts Worldwide, was designed to take the temperature of the industry on current challenges and help analysts understand how industry leaders plan to overcome those challenges in the next several years. It builds on surveys Booz & Company has conducted of E.U. pharma executives over the past several years.

“Those of us who work with pharma companies to develop and implement commercialization strategies know very well the challenges of maximizing asset value in this new environment, where both key customers and customer expectations are being redefined,” observes Susan McDonald, CEO of National Analysts Worldwide and leader of the firm’s healthcare practice. “We’re not surprised to hear people acknowledge that they can’t count on doing ‘business as usual’ and that they’re looking for new ways to gain traction.”

The greatest challenges identified by survey respondents are the growing healthcare system price/budget pressures and an increasing need to demonstrate cost-effectiveness and outcomes. In response to these challenges, more than half of the respondents expect to invest more heavily in marketing to key provider accounts and payors. Among the strategies seen as most important are new approaches to pricing, new service models, and new collaborations with payors.

Those convinced that the model is broken are reacting by making significant changes in how they spend marketing dollars and time. They are shifting their spending dramatically from community physicians to new stakeholders. In particular, they are disproportionately investing in key accounts, payors, and hospital stakeholders. By contrast, those who are not convinced the model is broken are making few adjustments to their spending.

“The pharmaceutical industry is the eye of a hurricane of change. The sales and marketing model is being forced to move to one that is much more complex. And this is happening in an uncertain market with incredible pressure to reduce budgets. The only clear path out of the storm is for companies to identify and focus on building the few critical capabilities they will need to succeed,” says Danielle Rollmann, a partner in Booz & Company’s global health practice.

The survey provides insights into the capabilities and strategies that will be most important moving forward, including:

- Organizing sales and marketing activities around diverse stakeholders, especially hospitals and insurers
- Taking a more creative approach to customer collaboration, including new pricing strategies, innovative service models, and novel partnerships
- Doing a more effective job of demonstrating value through outcomes
- Continuing to emphasize direct-to-consumer (DTC) marketing, in recognition that patients hold the other end of the purse strings
- More effectively using innovative digital media channels

“Virtually everything is changing in the model and the market. In response, most respondents say they plan to spend more on

all their target marketing activities. Yet this is not aligned with what pharma is doing and needs to do at a company level. The companies that focus, prioritize, and follow a coherent strategy will be the winners,” says Rolf Fricker, a Munich-based partner at Booz & Company.

As noted above, the survey also signals plans to do more direct-to-consumer marketing. “This is one of many areas where we are helping pharmaceutical companies think differently. The power base in the industry is fundamentally shifting toward insurance companies, integrated providers, and patients. Influencing a sale is getting increasingly complicated and requires more innovative approaches to reach multiple audiences, so expect to see more innovative digital and social media in this space,” says David Levy, a partner at Booz & Company serving clients in the life sciences.

The survey, which was completed in late fall 2011, is based on a sample of 156 sales and marketing leaders, most with global responsibilities, at pharmaceutical companies in the U.S. and E.U. Survey participants were primarily vice presidents and directors. For a link to the key findings of the survey, visit: <http://www.booz.com/media/uploads/BoozCo-Pharmaceutical-Sales-Marketing-Trends-National-Analysts-2011.pdf>

SOURCE: Booz & Company



Probe Proteins Ultrafast with Infrared Spectroscopy

Structure–functional relationships have always been central to understanding biology at the molecular and cellular level. Analyzing protein structure can tell scientists a great deal about how a protein behaves, but many of the methods now used to study structure require proteins to be crystallized or otherwise altered from their natural state.

Now, MIT researchers have developed a way to analyze proteins that doesn't require any pre-treatment. The technique is also extremely fast, allowing scientists to see, for the first time, how a protein changes its shape over picoseconds, or trillionths of a second.

The researchers, led by chemistry professor Andrei Tokmakoff and postdoc Carlos Baiz, describe their new technique this month in the journal *Analyst*. Their approach

builds on a technology known as two-dimensional infrared spectroscopy, which works by shining pulses of infrared light on a molecule and measuring the resulting molecular vibrations. In the new paper, the researchers came up with a way to analyze that data and correlate it with common structural elements found in proteins.

Once assembled, proteins tend to fold into one of two secondary structures, known as alpha helices and beta pleated sheets. In this study, the researchers distinguished between those two structures by examining how bonds between carbon and oxygen — found in each of the amino acids that make up proteins — vibrate when exposed to infrared light.

In an alpha helix, the carbon-oxygen bonds run parallel to the protein's backbone; in a beta sheet, those bonds are perpendicular

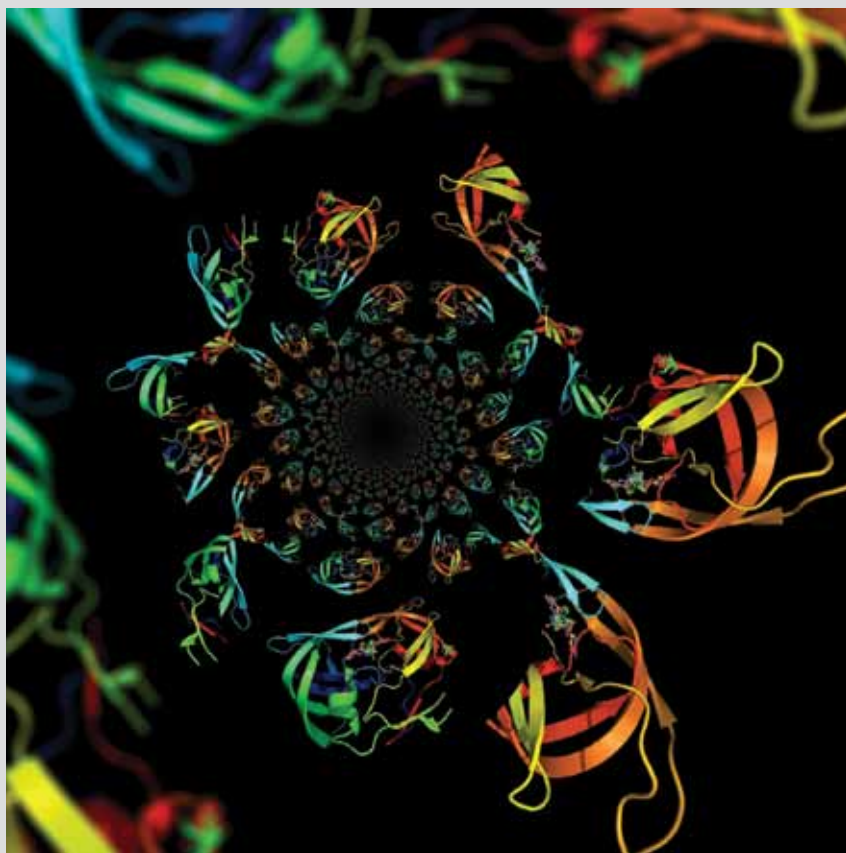
to the sheet. Because of that difference, the bonds vibrate at different frequencies when struck with infrared light. This allows the researchers to calculate the percentage of the amino acids that belong to a helical structure and the percentage that form a beta sheet.

The researchers confirmed the accuracy of their calculations by analyzing a set of proteins whose structures are already known. Their method does not currently reveal the exact structure of a protein, but the researchers are working on ways to determine the arrangements of the sheets and helices from the spectroscopic data. "In principle, the full structure of the protein is represented in the spectrum. The trick is how to get out the information," says Baiz, lead author of the paper.

One way to do that is to analyze data from a broader range of infrared wavelengths. The researchers are also developing methods to get information about other bonds within the amino acids. Because the new method can be performed over millionths of a second, it can be used to study how proteins fold and unfold when denatured by heat. After hitting a protein with a laser blast to heat it up, the researchers can capture a series of snapshots of how the protein unfolds over this very short time period.

"This is the first method that will allow us to take snapshots of the structure of the protein as it's denatured," Baiz says. "Usually the way people look at proteins is they start with the unfolded state and they end up with the folded state, so you have two static structures. What we can do now is look at all the structures along the pathway."

As the technique can now track structural changes over time, it would be particularly useful for studying proteins that cause disease when misfolded, such as the tau protein found in patients with Alzheimer's disease and the prion that causes Creutzfeldt-Jakob disease. The method can also measure the structural changes that occur as proteins bind to each other.



This DNA Cannot be Replicated

Appplied DNA Sciences, Inc. (OTCBB: APDN), a provider of DNA-based security, anti-counterfeiting technology, law-enforcement and product-authentication solutions, and Holliston LLC, announced they are working together to develop the next generation security platform for various product coatings, including passports and luxury packaging materials, with botanical SigNature DNA®. As the nation's oldest and largest manufacturer of cloth coverings, Holliston has served the book cover material, packaging fabric, and industrial cloth markets since 1895. Holliston remains the U.S. Government's preferred supplier of high-security passport cover material.

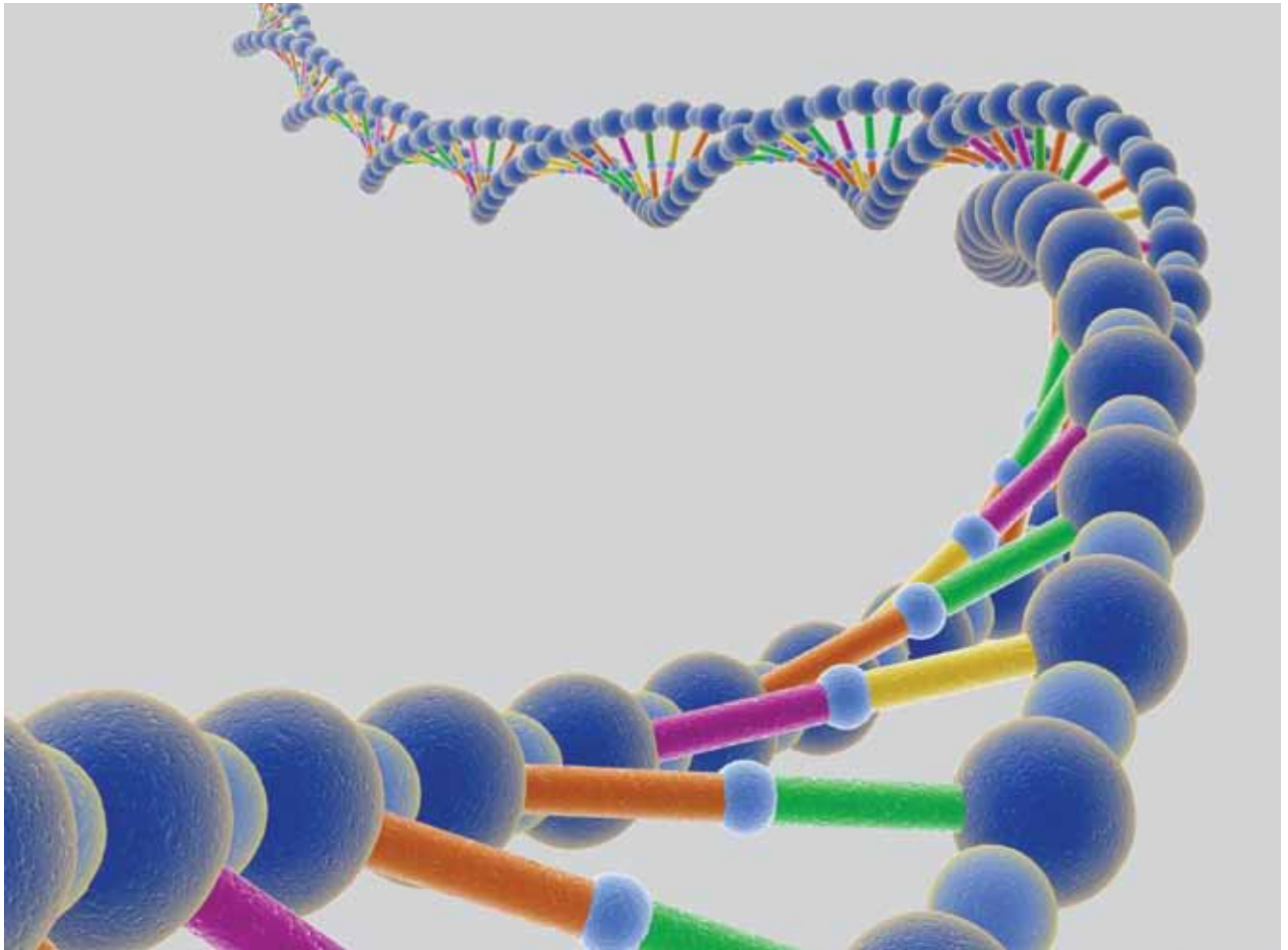
Holliston's Chief Operating Officer, Keith Polak, stated: "We are excited about the prospect of incorporating the botanical

SigNature DNA layer into a variety of products to stem the rising threat of forged passports and other identity documents. DNA, we believe, is the gold standard, and we are working toward providing our customers with the best security solution, whilst maintaining the highest quality products to which they are accustomed."

Applied DNA Sciences and Holliston are developing and testing DNA-coatings that essentially cannot be copied, and provide a means for customs and law enforcement groups to authenticate products in the field, and in the lab. The joint work has resulted in a feasibility study that successfully demonstrated the ability to incorporate botanical SigNature DNA onto passport covers. The next phase of the collaboration is to develop working prototypes, and move toward scaling up the process for commercial production.

Dr. James Hayward, APDN CEO and President, stated: "Passport authenticity governs secure entry into the United States for all citizens and visitors. We are pleased to be working with Holliston, the world's largest supplier of secure passport bindings. This effort extends our existing business to enhance government security."

APDN is a provider of botanical-DNA based security and authentication solutions that can help protect products, brands and intellectual property of companies, governments and consumers from theft, counterfeiting, fraud and diversion. SigNature® DNA and smartDNA™, its principal anti-counterfeiting and product authentication solutions that essentially cannot be copied, provide a forensic chain of evidence and can be used to prosecute perpetrators.



New Single-Cell, Single-Molecule Method to Identify DNA



Researchers at NYU and UCLA have developed a method to detect sequence differences in individual DNA molecules by taking nanoscopic pictures of the molecules themselves.

Using the approach they call "Direct Molecular Recognition," the UCLA and NYU researchers used nanoparticles to turn the DNA molecules into a form of molecular braille that can be read in the scale of nanometers, or one billionth of a meter, using high-speed Atomic Force Microscopy (AFM).

The leaders of the study are: Jason Reed, a research professor, and Professor Jim Gimzewski, nanotechnology pioneer, both at UCLA's California Nanosystems Institute, and Professor Bud Mishra, genomics expert, at NYU's Courant Institute of Mathematical Sciences. This group believes the method will have many practical uses, such as super-sensitive detection of DNA molecules in genomic research and medical diagnostics

as well as in identifying pathogens.

While there are already a variety of techniques used for this purpose, they are time consuming, technically difficult, and expensive. They also require a large amount of genetic material in order to obtain accurate readings and often require prior knowledge of the sample composition. To overcome these shortcomings, the team devised a "single-cell, single-molecule" method that would dispense with the complex chemical manipulations on which existing methods are based, and, instead, utilize the unique shapes of the molecules themselves as the method of identification. This approach has the benefits of being rapid and sensitive to the level of a single molecule.

Reed says that "the long term goal of our team's research is to dissect, understand, and control the biology of single cells in complex tissues, such as brain, or in

malignant tumors. Furthering this body of work requires that we address an unsolved problem in single-cell molecular analysis: the lack of a method to routinely, reliably, and inexpensively determine global gene transcriptional activity."

In their paper, the team closely examined the potential use of this technique to quantify the activity of genes in living tissue, a method known as transcriptional profiling. They were able to show that their Direct Molecular Recognition technique could accurately quantitate the relative abundance of multiple DNA species in a mixture using only a handful of molecules – a result not achievable using other methods.

The work is reported in the *Journal of the Royal Society Interface*. Their study was supported by a grant from the National Institute of General Medical Sciences, part of the National Institutes of Health.

New Gene Therapy Approach Could Treat Sick Cell

A team of researchers led by scientists at Weill Cornell Medical College has designed what appears to be a powerful gene therapy strategy that can treat both beta-thalassemia disease and sickle cell anemia. They have also developed a test to predict patient response before treatment.

This study's findings, published in *PLoS ONE*, represents a new approach to treating these related, and serious, red blood cells disorders, say the investigators.

"This gene therapy technique has the potential to cure many patients, especially if we prescreen them to predict their response using just a few of their cells in a test tube," says the study's lead investigator, Dr. Stefano Rivella, Ph.D., an associate professor of genetic medicine at Weill Cornell Medical College. He led a team of 17 researchers in three countries.

Dr. Rivella says this is the first time investigators have been able to correlate the outcome of transferring a healthy beta-globin gene into diseased cells with increased production of normal hemoglobin — which has long been a barrier to effective treatment of these disease. So far, only one patient in France has been treated with gene therapy for beta thalassemia, and Dr. Rivella and his colleagues believe the new treatment they developed will be a significant improvement. No known patient has received gene therapy yet to treat sickle cell anemia.

Beta-thalassemia is an inherited disease caused by defects in the beta-globin gene. This gene produces an essential part of the hemoglobin protein, which, in the form of red blood cells, carries life-sustaining oxygen



throughout the body. The new gene transfer technique developed by Dr. Rivella and his colleagues ensures that the beta-globin gene that is delivered will be active, and that it will also provide more curative beta-globin protein. "Since the defect in thalassemia is lack of production of beta-globin protein in red blood cells, this is very important," Dr. Rivella says.

The researchers achieved this advance by hooking an "ankyrin insulator" to the beta-globin gene that is carried by a lentivirus vector. During the gene transfer, this vector would be inserted into bone marrow stem cells taken from patients, and then delivered back via a bone marrow transplant. The stem cells would then produce healthy beta-globin protein and hemoglobin.

This ankyrin insulator achieves two goals. First, it protects delivery of the normal beta-globin gene. "In many gene therapy applications, a curative gene is introduced into the cells of patients in an indiscriminate fashion," Dr. Rivella explains. "The gene lands randomly in the genome of the patient, but where it lands is very important because not all regions of the genome are the same."

For example, some therapeutic genes may land in an area of the genome that is normally silenced — meaning the genes in this area are not expressed. "The role of ankyrin insulator is to create an active area in the genome where the new gene can work efficiently no matter where it lands," Dr. Rivella says. He adds that the small insulator used in his vector should eliminate the kind of side effects seen in the French patient treated with beta-thalassemia gene therapy.

The research team also discovered that the insulator increases the efficiency by which the beta-globin gene is transcribed during the process of making the red blood cells. "We found the gene is integrated into cells which have not yet begun to make red blood cells, and when they do, the beta-globin gene is activated," Dr. Rivella says. "We showed that if the insulator is present, activation of the curative gene is more efficient. This provides more curative protein to red blood cells."

The study further provides evidence that the vector had different rates of efficiency depending on the beta-thalassemia mutation

it was used in — thus providing the basis for a predictive test in patients. The investigators tested 19 different beta-thalassemia samples comprising the two types commonly found in patients — "beta-zero" cells that do not produce any beta-globin (forcing patients to receive blood transfusions throughout life), and "beta-plus" cells that produce suboptimal levels of hemoglobin. On average, they found that one copy of the vector in beta-zero cells produced 55 percent of the adult hemoglobin seen in normal individuals. Beta-plus cells, after treatment, produced hemoglobin comparable to a healthy individual, and were thus cured.

"The variable nature of the beta-thalassemia mutations suggests that some patients would be better candidates for gene therapy than others, and that success of gene therapy depends on the ability of a specific vector to make hemoglobin," Dr. Rivella says. "This is something we can test in advance using a little bit of a patient's blood — which is quite extraordinary."

The issue in sickle cell anemia is very different, Dr. Rivella says. The hemoglobin protein is made in the right quantities, but it is not normal — the red cell is shaped like a sickle and is abnormal in function. "One of the problem in gene therapy of sickle cell anemia is to add a new gene without increasing too much the total amount of protein, both normal and sickle. This would cause other problems," he says.

By treating eight cell specimens taken from sickle cell anemia patients, the investigators discovered that attaching the ankyrin insulator to a normal beta-globin gene increases the amount of normal beta-globin protein while reducing the quantity of sickled protein. "The total amount of protein stays the same, which is very important," says first author Dr. Laura Breda, pediatric research associate at Weill Cornell Medical College.

These advances will likely make a substantial impact on a number of fields, including gene regulation and transfer and the design of gene therapy trials. "This study represents a fresh departure from previously published work in the field of gene therapy," Dr. Rivella says. The *PLoS ONE* article may be found online at [after the embargo lifts](#).

Clamor Affects More than Birds and Other Animals

For some years, scientists have known that birds and other animals change their behavior in response to human noise, such as the din of traffic or the hum of machinery. The case of birds imitating mobile phone ringtones is just one of several well-known examples.

But human clamor does not just affect animals. As many animals also pollinate plants or eat or disperse their seeds, human noise can have indirect effects on plants, too, finds a new study reported in the March 21, 2012, issue of the journal *Proceedings of the Royal Society B*.

In cases where noise has ripple effects on long-lived plants like trees, the consequences could last for decades, even after the source of the noise goes away, says lead author Clinton Francis of the National Science Foundation (NSF) National Evolutionary Synthesis Center in Durham, North Carolina.

In previous studies, Francis and colleagues found that some animals increase in numbers near noisy sites, while others decline. To find out if animals' different responses to human noise have indirect effects on plants, the researchers conducted a series of experiments from 2007 to 2010 in the Bureau of Land Management's Rattlesnake Canyon Wildlife Area in northwestern New Mexico. The region is home to thousands of natural gas wells, many of which are coupled with noisy compressors for extracting the gas and transporting it through pipelines. The compressors roar and rumble day and night, every day of the year. The advantage of working in natural gas sites is they allow scientists to study noise and its effects on wildlife without the confounding factors in noisy areas like roadways or cities, such as pollution from artificial light and chemicals, or collisions with cars.

As part of their research, Francis and colleagues first conducted an experiment using patches of artificial plants designed to mimic a common red wildflower in the area called scarlet gilia. Each patch consisted of five artificial plants with three "flowers" each--microcentrifuge tubes wrapped in red electrical tape--which were filled with

a fixed amount of sugar water for nectar.

To help in estimating pollen transfer within and between the patches, the researchers also dusted the flowers of one plant per patch with artificial pollen, using a different color for each patch. Din levels at noisy patches were similar to that of a highway heard from 500 meters away, Francis said. When the researchers compared the number of pollinator visits at noisy and quiet sites, they found that one bird species in particular--the black-chinned hummingbird--made five times more visits to noisy sites than quiet ones.

"Black-chinned hummingbirds may prefer noisy sites because another bird species that preys on their nestlings, the western scrub jay, tends to avoid those areas," Francis said. Pollen transfer was also more common in the noisy sites. If more hummingbird visits and greater pollen transfer translate to higher seed production for the plants, the results suggest that "hummingbird-pollinated plants such as scarlet gilia may indirectly benefit from noise," Francis said.

Another set of experiments revealed that noise may indirectly benefit some plants, but is bad news for others. In a second series of experiments at the same study site, the researchers set out to discover what noise might mean for tree seeds and seedlings, using one of the dominant trees in the area--the piñon pine. Piñon pine seeds that aren't plucked from their cones fall to the ground and are eaten by birds and other animals.

To find out if noise affected the number of piñon pine seeds that animals ate, the researchers scattered piñon pine seeds beneath 120 piñon pine trees in noisy and quiet sites, using a motion-triggered camera to figure out what animals took the seeds. After three days, several animals were spotted feeding on the seeds, including mice, chipmunks, squirrels, birds and rabbits.

But two animals in particular differed between quiet and noisy sites--mice, which preferred noisy sites, and western scrub jays, which avoided them altogether. Piñon pine seeds that are eaten by mice don't survive the passage through the animal's gut, Francis

said, so the boost in mouse populations near noisy sites could be bad news for pine seedlings in those areas.

In contrast, a single western scrub jay may take hundreds to thousands of seeds, only to hide them in the soil to eat later in the year. The seeds they fail to relocate will eventually germinate, so the preference of western scrub jays for quiet areas means that piñon pines in those areas are likely to benefit.

In keeping with their seed results, the researchers counted the number of piñon pine seedlings and found that they were four times as abundant in quiet sites compared with noisy ones.

It may take decades for a piñon pine to grow from a seedling into a full-grown tree, Francis said, so the consequences of noise may last longer than scientists thought.

"Fewer seedlings in noisy areas might eventually mean fewer mature trees, but because piñon pines are so slow-growing the shift could have gone undetected for years," he said. "Fewer piñon pine trees would mean less critical habitat for the hundreds of species that depend on them for survival." Other authors of the study include Catherine Ortega, most recently of Fort Lewis College, and Alexander Cruz and Nathan Kleist of the University of Colorado, Boulder.



The End of RNA World?

In the beginning – of the ribosome, the cell's protein-building workbench – there were ribonucleic acids, the molecules we call RNA that today perform a host of vital functions in cells. And according to a new analysis, even before the ribosome's many working parts were recruited for protein synthesis, proteins also were on the scene and interacting with RNA. This finding challenges a long-held hypothesis about the early evolution of life.

University of Illinois crop sciences and Institute for Genomic Biology professor Gustavo Caetano-Anollés led a study that used molecular analyses to determine the evolutionary histories of the proteins and the RNAs that make up the ribosome. The study appears in the journal *PLoS ONE*.

The "RNA world" hypothesis, first promoted in 1986 in a paper in the journal *Nature* and defended and elaborated on for more than 25 years, posits that the first stages of molecular evolution involved RNA and not proteins, and that proteins (and DNA) emerged later, said University of Illinois crop sciences and Institute for Genomic Biology professor Gustavo Caetano-Anollés, who led the new study.

"I'm convinced that the RNA world (hypothesis) is not correct," Caetano-Anollés said. "That world of nucleic acids could not have existed if not tethered to proteins." The ribosome is a "ribonucleoprotein machine," a complex that can have as many as 80 proteins interacting with multiple RNA molecules, so it makes sense that this assemblage is the result of a long and complicated process of gradual co-evolution, Caetano-Anollés said. Furthermore, "you can't get RNA to perform the molecular function of protein synthesis that is necessary for the cell by itself."

Proponents of the RNA world hypothesis make basic assumptions about the evolutionary origins of the ribosome without proper scientific support, Caetano-Anollés said. The most fundamental of these

assumptions is that the part of the ribosome that is responsible for protein synthesis, the peptidyl transferase center (PTC) active site, is the most ancient.

In the new analysis, Caetano-Anollés and graduate student Ajith Harish (now a postdoctoral researcher at Lund University in Sweden) subjected the universal protein and RNA components of the ribosome to rigorous molecular analyses – mining them for evolutionary information embedded in their structures. (They also analyzed the thermodynamic properties of the ribosomal RNAs.)

They used this information to generate timelines of the evolutionary history of the ribosomal RNAs and proteins.

These two, independently generated "family trees" of ribosomal proteins and ribosomal RNAs showed "great congruence" with one another, Caetano-Anollés said. Proteins surrounding the PTC, for example, were as old as the ribosomal RNAs that form that site. In fact, the PTC appeared in evolution just after the two primary subunits that make up the ribosome came together, with RNA bridges forming between them to stabilize the association.

The timelines suggest that the PTC appeared well after other regions of the protein-RNA complex, Caetano-Anollés said. This strongly suggests, first, that proteins were around before ribosomal RNAs were recruited to help build them, and second, that the ribosomal RNAs were engaged in some other task before they picked up the role of aiding in protein synthesis, he said.

"This is the crucial piece of the puzzle," Caetano-Anollés said. "If the evolutionary buildup of ribosomal proteins and RNA and the interactions between them occurred gradually, step-by-step, the origin of the ribosome cannot be the product of an RNA world. Instead, it must be the product of a ribonucleoprotein world, an ancient world that resembles our own. It appears the basic

building blocks of the machinery of the cell have always been the same from the beginning of life to the present: evolving and interacting proteins and RNA molecules."

"This is a very engaging and provocative article by one of the most innovative and productive researchers in the field of protein evolution," said University of California at San Diego research professor Russell Doolittle, who was not involved in the study. Doolittle remains puzzled, however, by "the notion that some early proteins were made before the evolution of the ribosome as a protein-manufacturing system." He wondered how – if proteins were more ancient than the ribosomal machinery that today produces most of them – "the amino acid sequences of those early proteins were 'remembered' and incorporated into the new system."

Caetano-Anollés agreed that this is "a central, foundational question" that must be answered. "It requires understanding the boundaries of emergent biological functions during the very early stages of protein evolution," he said. However, he said, "the proteins that catalyze non-ribosomal protein synthesis – a complex and apparently universal assembly-line process of the cell that does not involve RNA molecules and can still retain high levels of specificity – are more ancient than ribosomal proteins. It is therefore likely that the ribosomes were not the first biological machines to synthesize proteins."

Caetano-Anollés also noted that the specificity of the ribosomal system "depends on the supply of amino acids appropriately tagged with RNA for faithful translation of the genetic code. This tagging is solely based on proteins, not RNAs," he said. This suggests, he said, that the RNA molecules began as co-factors that aided in protein synthesis and fine-tuned it, resulting in the elaborate machinery of the ribosome that exists today.

Curly Leaves Inspire New Technique for Shaping Thin Gel Sheets

Inspired by nature's ability to shape a petal, and building on simple techniques used in photolithography and printing, researchers at the University of Massachusetts Amherst have taken biomimicry to a whole new level. Their new tool for manufacturing three-dimensional shapes easily and cheaply, can aid advances in biomedicine, robotics and tunable micro-optics.

Ryan Hayward, Christian Santangelo and colleagues describe their new method of halftone gel lithography for photo-patterning polymer gel sheets in the current issue of *Science*. They say the technique, among other applications, may someday help biomedical researchers to direct cells cultured in a laboratory to grow into the correct shape to form a blood vessel or a particular organ.

"We wanted to develop a strategy that would allow us to pattern growth with some of the same flexibility that nature does," Hayward explains. Many plants create curves, tubes and other shapes by varying growth in adjacent areas. While some leaf or petal cells expand, other nearby cells do

not, and this contrast causes buckling into a variety of shapes, including cones or curly edges. A lily petal's curve, for example, arises from patterned areas of elongation that define a specific three-dimensional shape.

Building on this concept, Hayward and colleagues developed a method for exposing ultraviolet-sensitive thin polymer sheets to patterns of light. The amount of light absorbed at each position on the sheet programs the amount that this region will expand when placed in contact with water, thus mimicking nature's ability to direct certain cells to grow while suppressing the growth of others. The technique involves spreading a 10-micrometer-thick layer (about 5 times thinner than a human hair) of polymer onto a substrate before exposure.

Areas of the gel exposed to light become crosslinked, restricting their ability to expand, while nearby unexposed areas will swell like a sponge as they absorb water. As in nature, this patterned growth causes the gel to buckle into the desired shape. Unlike in nature, however, these materials can be repeatedly flattened and re-shaped by drying out and rehydrating the sheet.

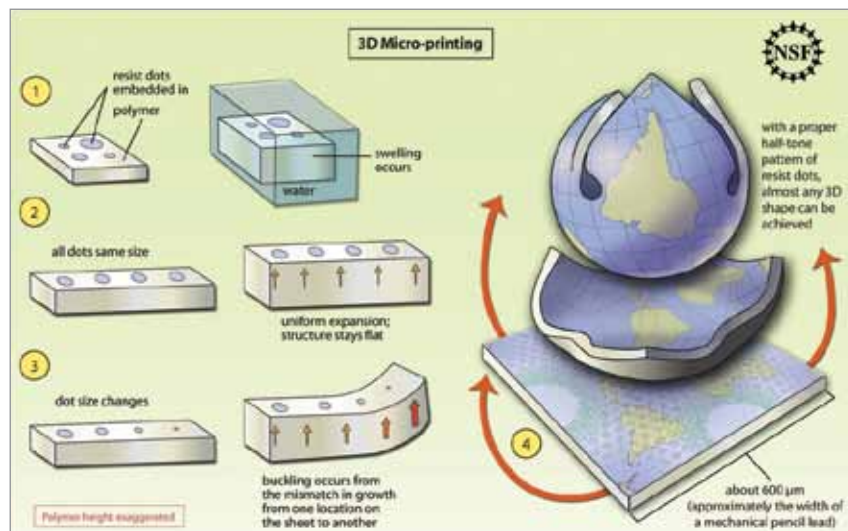
To date, the UMass Amherst researchers have made a variety of simple shapes including spheres, saddles and cones, as well as more complex shapes such as minimal surfaces. Creating the latter represents a fundamental challenge that demonstrates basic principles of the method, Hayward says.

Santangelo and Hayward also borrowed an idea from the printing industry that allows them to make complicated patterns in a very simple way. In photolithography, just as in printing, it is expensive to print a picture using different color shades because each shade requires a different ink. Thus, most high-volume printing relies on "halftoning," in which only a few ink colors are used to print varied-sized dots. Smaller dots take up less space and allow more white light to reflect from the paper, so they appear as a lighter color shade than larger dots.

An important discovery by the UMass Amherst team is that this concept applies equally well to patterning the growth of their gel sheets. Rather than trying to make smooth patterns with many different levels of growth, they were able to simply print dots of highly restricted growth and vary the dot size to program a patterned shape.

"We're discovering new ways to plan or pattern growth in a soft polymer gel that's spread on a substrate to get any shape you want," Santangelo says. "By directly transferring the image onto the soft gel with half-tones of light, we direct its growth."

He adds, "We aren't sure yet how many shapes we can make this way, but for now it's exciting to explore and we're focused on understanding the process better. A model system like this helps us to watch how it unfolds. For biomedicine or bioengineering, one of the questions has been how to create tissues that could help to grow you a new blood vessel or a new organ. We now know a little more about how to go from a flat sheet of cells to a complex organism."



Mutant Plants May be Better for Biofuels

Genetic mutations to cellulose in plants could improve the conversion of cellulosic biomass into biofuels, according to a research team that included two Iowa State University chemists.

The team recently published its findings in the online early edition of the Proceedings of the National Academy of Sciences. Mei Hong, an Iowa State professor of chemistry and an associate of the U.S. Department of Energy's Ames Laboratory, and Tuo Wang, an Iowa State graduate student in chemistry, contributed their expertise in solid-state nuclear magnetic resonance spectroscopy to the study.

The study was led by Seth DeBolt, an associate professor of horticulture at the University of Kentucky in Lexington. Chris Somerville, the Philomathia Professor of Alternative Energy and director of the Energy Biosciences Institute at the University of California, Berkeley, is also a contributing author. The research project was supported by grants from the National Science Foundation and the U.S. Department of Energy.

Researchers studied *Arabidopsis thaliana*, a common model plant in research studies, and its cellulose synthase membrane complex that produces the microfibrils of cellulose that surround all plant cells and form the basic structure of plant cell walls.

These ribbons of cellulose are made of crystallized sugars. The crystal structure makes it difficult for enzymes to break down the cellulose to the sugars that can be fermented into alcohol for biofuels. And so DeBolt assembled a research team to see if genetic mutations in the plant membrane complex could produce what the researchers have called "wounded" cellulose that's not as crystalline and therefore easier to break down into sugar.

Hong, who had done previous studies of plant cell walls, used her lab's solid-state nuclear magnetic resonance technology to study the cell walls created by the mutated system. The goals were to collect as much information as possible about the molecular structure of the cell walls to see if mutations to the plants resulted in changes to the cellulose. "We found that the crystalline

cellulose content had decreased in the mutant cell walls," Hong said. "We can quantify the degree of change, and be very specific about the type of change."

The cellulose microfibrils in the mutant cell walls, for example, were thinner than those found in normal plants, Hong said. The studies also found an additional type of cellulose with an intermediate degree of crystal structure. Hong said those findings suggest the genetic mutations did create differences in cellulose production and formation. The study also reports the cellulose produced by the mutated plant could be more efficiently processed into the sugars necessary for biofuel production.

"What this work suggests, in very broad terms, is that it is possible to modify cellulose structure by genetic methods, so that potentially one can more easily extract cellulose from plants as energy sources," Hong said. The research team's paper said developing techniques to modify the structure of plant cellulose in crops for better and easier conversion to fermentable sugars "could be transformative in a bio-based economy."

Breakthrough in ID'ing Target Cancer Epigenetic Genes

Cancer is usually attributed to faulty genes, but a growing mass of evidence from the field of cancer epigenetics indicates a key role for the gene "silencing" proteins that stably turn genes off inside the cell nucleus. A new study from Rice University and Baylor College of Medicine (BCM) promises to speed research in the field by rapidly identifying the genes that epigenetic proteins can target for silencing.

The study, which appears this week in *Nucleic Acids Research*, shows how a new computer program called EpiPredictor can search any genome to identify specific genes affected by epigenetic proteins. The research includes detailed experimental findings that verify EpiPredictor's results. The research was funded in part by the Cancer Prevention

Research Institute of Texas (CPRIT).

In work that could shed light on the molecular workings of cancer cells, researchers from Rice University and Baylor College of Medicine have developed a method to rapidly identify genes that can be targeted for silencing. The team includes (clockwise from left) Qinghua Wang, Jianpeng Ma, Brian Kirk, Jia Zeng and Yufeng Gou.

"Cancer epigenetics is a new field, and we are still struggling with the basics," said lead investigator Jianpeng Ma, professor of bioengineering at Rice and the Lodwick T. Bolin Professor of Biochemistry at BCM. "It's something like a board game. Until now, we've understood some of the rules and seen a few of the pieces, but the game board itself has been mostly blank. EpiPredictor

lets everyone see the board. It really changes things."

While many cancers have been linked to mutations in the DNA sequence of particular genes, epigenetic changes do not involve genetic mutations. Instead, epigenetics allows two cells with identical DNA sequences to behave in wholly different ways. Epigenetic proteins effectively edit the genome by turning off genes that are not needed. This editing process is what allows human beings to have specialized cells — like nerve cells, bone cells and blood cells — that look and behave differently, even though they share the same DNA.

The key epigenetic players in cancer are a family of proteins called polycomb-group (PcG) proteins. PcGs are found deep inside the nucleus of cells, in the chamber

where DNA is stored. Studies have found abnormally high levels of PcGs in some of the most aggressive forms of breast and prostate cancer.

PcGs are generalists that can be called upon to silence any one of several hundred to several thousand genes. They are recruited to this task by polycomb response elements (PREs), segments of DNA that are located next to the genes the proteins subsequently silence. This is where the playing board goes blank; though scientists know there are literally hundreds to thousands of potential PREs in any given genome – including everything from simple insects to human beings – only a few PREs have ever been found.

"So far, only two PREs have been experimentally verified in mammals – one in mice and one in humans," said EpiPredictor creator Jia Zeng, a BCM postdoctoral research associate. "We suspect there are so many of them, but finding them has been difficult." Zeng, a computer scientist, had no formal biology training when she joined Ma's laboratory under a CPRIT-funded training program for computational cancer research.

"One of the biggest challenges since the completion of the Human Genome Project has been how to dig useful information out of the enormous amount of genomic data," Ma said.

Ma said Zeng's new method for zeroing in on PRE sequences is broadly applicable

for genomic data mining in areas beyond cancer research.

"Determining the function of a gene based solely on sequence data is virtually impossible," Ma said. "Recognizing this, Jia applied some advanced tools from computer science to create a learning program that could be trained to look for PRE sequences based upon the scant experimental data that were available."

In tests on the genome of the fruit fly *Drosophila melanogaster*, the EpiPredictor program found almost 300 epigenetic target genes. Experimental research by Ma's longtime collaborator, BCM biochemist Qinghua Wang, verified that the EpiPredictor predictions were biologically significant.

"We are now working on using the method to scan the human genome to search for potential genes that play a role in cancer epigenetics," said Wang, assistant professor of biochemistry and molecular biology. "We also hope that others will explore how this new method may help to identify the location and function of genes beyond the realm of epigenetics."

Co-authors include Rice graduate students Yufeng Gou and Brian Kirk, a predoctoral training fellow in the National Library of Medicine Training Program of the Keck Center of the Gulf Coast Consortia. The research was supported by the National Institutes of Health, the National Science Foundation, the Welch Foundation and the John and Ann Doerr Fund for Computational Biomedicine at the Ken Kennedy Institute for Information Technology, Rice University. Zeng's CPRIT fellowship is administered by the Keck Center Computational Cancer Biology Training Program of the Gulf Coast Consortia.

