Unveiling Vaccines

Vaccines: Where are we headed?

Cancer Vaccines – History, Recent Breakthroughs and Commercial Perspectives

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Vaccinating Asia

The 21st century has placed its spotlight on Asia in the field of vaccine developments as the result of a number of outbreaks and pandemics that swept across Asia. As Asia becomes an increasingly important marketplace, the Asian outbreaks in the beginning of the 21st century made its way into the Western world. The bout of epidemics and pandemics in Asia began when Dr. Carlo Urbani identified severe acute respiratory syndrome (SARS) as a new disease in 2003 when he diagnosed it in a 48-year-old American businessman who had traveled from the Guangdong province of China, through Hong Kong, to Vietnam. By early 2003, individuals from 37 countries had been infected by the virus. Following that, in the same year, Asia came under attack with the outbreak of the H5N1 Avian Flu – the most highly pathogenic strain which finally made its way to the West in 2005.

Globalization has made it much easier for transmission of disease. Although the Swine Flu of 2009 began in the United States and Mexico, by mid-year, China reported 318 cases whereas Japan reported 605 cases. As Asia’s consumer driven demands and public health continuously grows, it has become ever more important to form strategic partnerships both in research and development as well as trials and manufacturing. This was also the two key themes discussed during the 6th Annual World Vaccine Congress Asia this year. Such collaborations have given birth to antivirals such as Tamiflu and Relenza. The search is still on for SARS vaccines and improving on flu vaccines for H5N1. Another step is to study the influenza virus spread from the Southern Hemisphere and apply the data to the Northern Hemisphere so as to predict the next potential seasonal flu outbreak. Much of East and Southeast Asia is densely populated with people and livestock, providing the perfect collection of reservoirs for different strains to mix and mingle as well as undergo interspecies transmission from rural to city areas.

It is with that notion that in this month’s issue we begin with the question, "Where are we headed with vaccines?" through to an industry perspective on the vaccine industry and then a look into the latest technology developed to aid in vaccine development.

Sulastri Kamis
Editor
Asia Pacific Biotech News
Successful FDA end-of-Phase-2 for Hatchtech head lice product DeOVO™

Specialty pharmaceutical company Hatchtech Pty Ltd announced that it had successfully completed end-of-phase 2 (EOP2) consultations with the US Food & Drug Administration (FDA) for its lead product DeOvo™, a single application topical treatment for head lice.

This follows the recent successful completion of the phase 2b clinical trial demonstrating superior efficacy in 142 subjects with head lice infestation, 2 years of age and older at study centres in the United States.

The FDA reviewed Hatchtech’s current data package, phase 3 protocols and the readiness for phase 3 in all disciplines and provided assessments of the company’s detailed plans for the phase 3 development program. An EOP2 interaction with the FDA is a key part of seeking US marketing approval for prescription drug products.

Dr Lewis Schulz, Hatchtech’s chief operating officer said, “We appreciated the clear guidance from the FDA including the valuable, constructive feedback on several details of our pivotal study protocols. This reaffirms our proposed phase 3 program. Significantly there were no surprises and we were very encouraged by the responses to our questions. The Company remains on track to initiate the phase 3 program later this year.”

Hatchtech CEO Dr Ross Macdonald, commented: “This milestone is another important achievement for Hatchtech. With the FDA we have established a clear path to product registration and the market for DeOvo, our next-generation head lice treatment product that will provide compelling advantages over currently available treatments.”

Senz Oncology secures seed funding for promising cancer drug

Senz Oncology Pty Ltd (“Senz”) has secured seed investment from CoValence Inc (“CoValence”), a privately-held venture investment company in Menlo Park California, USA. Senz was established in February 2012 by experienced biotechnology executives, Dr. Ian Nisbet and Dr. Anthony Filippis, to develop new cancer drugs. Senz will use the seed investment to further the development of a novel chemotherapeutic agent, VAL-1000—in collaboration with California-based Allyence Research, Inc (“Allyence”).

VAL-1000 is an oral chemotherapeutic agent with very low toxicity, a potentially novel mechanism of action and a significant history of use in humans.

Senz and Allyence have identified a potential role for VAL-1000 in the treatment of acute leukemias, including acute myeloid leukemia (AML), having demonstrated significant activity in AML cell lines and primary tumours representing a range of disease genotypes. Each year approximately 1000 new cases of AML are diagnosed in Australia, making it the most common type of leukemia in adults.

“We are excited by the potential of VAL-1000 and enthusiastic to embark on clinical studies to establish its safety and efficacy in patients,” said Dr. Ian Nisbet, Senz Executive Director. “VAL-1000 may provide a completely new treatment option for AML, particularly in elderly patients who are unable to tolerate standard chemotherapeutic regimens.”

Senz’s mission is to provide new treatment options for cancer patients, leveraging the benefits of the Australian regulatory and taxation environment to provide time and cost effective drug development.

According to Dr. Anthony Filippis, Senz Executive Director, “A key driver for the creation of Senz was the number of opportunities identified through our consulting business, Afandin Pty Ltd, which assists life sciences companies and research institutes with corporate strategy and business development services.”

Investment in R&D, which is encouraged by the R&D tax incentive, is critical to the innovation that drives Australia’s productivity. According to Dr. Dennis Brown, President, Allyence “The R&D tax incentive and the clinical trial notification (CTN) scheme were critical elements in the decision to co-develop VAL-1000 with Senz.” Coincident with the seed investment from CoValence, Dr. Brown (who has previously founded companies such as Matrix Pharmaceuticals, Inc and ChemGenex Therapeutics, Inc) has joined the Senz Board as a Non-Executive Director.
South Australian biotechnology company, GeneWorks, has developed a new DNA barcoding technology for use as a security and authentication tool. Invisible marking using DNA is increasingly popular to identify and authenticate goods and deter intruders. GeneWorks has invented a method compatible with forensic analysis, unlike existing technologies currently on the market.

The worldwide counterfeiting technology and security market is worth over $82 billion, and includes a range of technologies used for anti-counterfeiting and authentication of high value products. DNA barcoding can be used to invisibly mark such items as banknotes, wine, pharmaceuticals, and art work. It can also be formulated as a fixative spray which allows it to be used to uniquely tag intruders upon entering a security protected premise and thus link them to the crime scene.

Current DNA barcoding technologies on the market are not compatible with forensic instrumentation which has limited their legal standing in court. The GeneWorks technology, however, can be analysed using existing techniques employed by forensic laboratories.

The technology employed involves a combination of DNA molecules of different defined lengths. These molecules are then mixed in a unique combination specific for a particular tagged item or premise.

"Compatibility with forensic instrumentation and DNA databases means that this technology can be used as evidence for criminal convictions in court," said Mr Rob King Business Development Manager at GeneWorks. "Applications of the technology are endless and are especially useful in industries such as apparel and pharmaceuticals where companies suffer loss of revenue and reputation damage due to counterfeiting."

The State government, through BioSA, has funded development of this new DNA barcoding technology that will initially undergo validation by Forensic Science SA, before scale up to produce sufficient codes for commercial use. There has already been increasing interest in the use of DNA for tagging purposes, both in Australia, Europe and the US, and GeneWorks hopes to tap into this growing market.

"Uptake of this technology will add to the growing list of exports from the high tech sector," said Dr Jurgen Michaelis, CE of BioSA. "We are increasingly seeing the economic value that can be derived from a well-supported and diverse technology sector in South Australia."
Glucocorticoids, a group of hormones that include cortisol, are considered stress hormones because their levels increase following stress. When their relationship to stress was first identified, it was shown that the release of cortisol prepared the body to cope with the physical demands of stress. Subsequently, high levels of cortisol were linked to depression and other stress-related disorders, giving rise to the hypothesis that high levels of cortisol on a long-term basis may impair the psychological capacity to cope with stress.

For this reason, drugs such as mifepristone that block glucocorticoid activity, called glucocorticoid receptor antagonists, have been tested as treatments for depression. But other recent data suggest that, in animal models and in humans, elevating glucocorticoid levels may reduce the development of posttraumatic stress disorder or PTSD.

This hypothesis is now supported by a new study in *Biological Psychiatry*. Using an animal model of PTSD, Rajnish Rao and colleagues demonstrate that elevated levels of glucocorticoids at the time of acute stress confers protection against the delayed enhancing effect of stress on synaptic connectivity in the basolateral amygdala and anxiety-like behavior.

"It seems, increasingly, that the ‘trauma’ in posttraumatic stress disorder is the impact of stress on brain structure and function," commented Dr. John Krystal, Editor of *Biological Psychiatry*. "The study by Rao and colleagues provides evidence that glucocorticoids may have protective effects in their animal model that prevent from these changes in synaptic connectivity, potentially shedding light on protective effects of glucocorticoids described in relation to PTSD."

Senior author Prof. Sumantra Chattarji from the National Centre for Biological Sciences in Bangalore, India explained the reasoning behind their work: "First, this work was inspired by a puzzle - counterintuitive clinical reports - that individuals having lower levels of cortisol are more susceptible to developing PTSD and that cortisol treatment in turn reduces the cardinal symptoms of PTSD. Second, using a rodent model of acute stress, we were not only able to capture the essence of these clinical reports, but also identify a possible cellular mechanism in the amygdala, the emotional hub of the brain."

Their results are consistent with clinical reports on the protective effects of glucocorticoids against the development of PTSD symptoms triggered by traumatic stress.

Two successive manipulations, both of which elevate corticosterone levels by themselves, together reset the number of synapses in the amygdala and restored anxiety behavior to normal levels in rats. Strikingly, these high and low numbers of synapses in the amygdala appear to be reliable predictors of high and low anxiety states respectively.

"With the increasing costs and suffering associated with PTSD victims, it is our hope that basic research of the kind reported in this study will help in developing new therapeutic strategies against this debilitating disorder," concluded Chattarji.
Results from a recent study of 1,000 women across 10 Asian countries, including Singapore, has revealed critical knowledge gaps about fertility, the key causes of infertility and fertility treatment options. Called Starting Families Asia*, the study is commissioned by Merck Serono, a division of Merck, Darmstadt, Germany, in collaboration with one of Asia’s leading fertility experts, Professor PC Wong, Senior Consultant and Head of the Division of Reproductive Endocrinology and Infertility at the National University Hospital (NUH) Women’s Centre. The largest study of its kind, Starting Families Asia has been endorsed by the Asia Pacific Initiative on Reproduction (ASPIRE).

Commenting on the findings of the study, Professor Wong said, “The results from Starting Families Asia could be indicative of the potential barriers to the help that women and couples should be seeking and receiving when planning to start a family; especially for those facing difficulty in conceiving. The study results also highlight that more public education and awareness on the impact of age and medical problems on fertility, as well as the treatment options available to patients who may be suffering from infertility, is vital.”

The Starting Families Asia study revealed that less than half of the women surveyed across the region understand that a couple is classified as infertile if they fail to conceive after one year of trying (43%); that a woman in her forties has a lower chance of falling pregnant than a woman in her thirties (36%); and that a healthy lifestyle does not necessarily guarantee fertility (32%). This could mean that many women are not seeking the help or treatment that could improve their chances of conceiving – particularly for women above age 35.

Many women believe that fate plays a part in fertility problems. In Singapore, 59% of women believe that infertility is “God’s will” and 42% attribute it to “bad luck”.

Many women believe that fate plays a part in fertility problems. In Singapore, 59% of women believe that infertility is “God’s will” and 42% attribute it to “bad luck”.
World’s first wearable robotic device for stroke rehabilitation comes to Singapore

Good news for stroke patients in Singapore! Kinesis Physio & Rehab is bringing in two new innovations to Singapore, which focus on stroke rehabilitation.

The first is the Tibion® Bionic Leg - the world's first wearable robotic device to aid stroke recovery. Stroke patients wear this device on their affected leg and work with a physiotherapist to perform exercises. This helps patients improve gait and balance, strengthen stance and enhance active motor learning. The second innovation is the ReJoyce Hand and Arm Rehabilitation system, which is a home-based therapy that can be supervised by therapists over the internet. The therapy involves a range of exercise games with adjustable difficulty levels, to maximise motor recovery of the hand, arm and shoulder. This is the first time that the Tibion Bionic Leg and ReJoyce Hand and Arm Rehabilitation system are being made available to the public in South East Asia, through Kinesis Physio & Rehab.

"Both the Tibion Bionic Leg and ReJoyce system work by encouraging stroke patients to repeat certain movements of their affected limbs in a regular and consistent manner. This supports the principles of neuroplasticity, which is the nervous system’s ability to renew and rewire itself, and this is crucial in recovering motor ability during stroke rehabilitation. At Kinesis Physio & Rehab, we combine the latest technologically-advanced equipment with our clinical experience, to offer optimal evidence-based solutions to help stroke patients regain mobility," said Philippe Steiner, Chief Executive Officer, Kinesis Physio & Rehab.

The Tibion Bionic Leg is a battery-powered robotic trainer consisting of a pressure-sensing shoe insert, motors to provide leg support, an angle sensor in the knee and a computer where the therapist can programme the level of intensity and monitor patients’ movements. Using the Tibion Bionic Leg, the patient initiates effort by applying weight to the affected foot/leg.

Sensors within the device detect this force and motors support the affected leg, aiding the patient in his/her ambulatory exercises. These exercises include moving from sitting-to-standing positions, overground walking and climbing up and down stairs. The physiotherapist alters the intensity of the therapy to ensure the patient works at optimal levels. As the patient’s strength and confidence increases, the physiotherapist reduces the level of assistance from the robotic device. Once the patient’s affected leg strength matches the unaffected leg, the patient continues exercises without intervention or assistance.

For optimal results, Kinesis Physio & rehab recommends stroke patients use the Tibion Bionic Leg constantly and frequently, at two to three times a week, for a minimum of 6 weeks. Ideally, this therapy would commence as soon after the stroke as possible, although therapists have seen positive results in patients several years post-stroke. Patients affected by other neurology conditions, such as traumatic brain injury, partial spinal cord injuries, multiple sclerosis and Parkinson’s disease, could also benefit from using the Tibion Bionic Leg.

The ReJoyce Hand and Arm Rehabilitation system is a hand, arm and shoulder exercise therapy, delivered as a home-based service with supervision from a therapist via the Internet. The ReJoyce Manipulandum acts like a large joystick with features such as a gripper, peg, jar lid and door handle. Sensors in the device measure movements and forces applied by the patient. To motivate patients to use the ReJoyce Manipulandum in the right manner, the system runs a range of games on a computer laptop. To progress in these games, patients must carry out upper limb exercises that represent activities of daily life. The therapist adjusts the games’ difficulty levels, as the patient’s abilities improve.

Kinesis Physio & Rehab recommends stroke patients use the ReJoyce Hand and Arm Rehabilitation system on a daily basis, with tele-supervised therapy sessions occurring once a week, for a minimum of 6 weeks. In addition to stroke, the ReJoyce system could benefit individuals suffering from spinal cord injury or brain injury. See Annex A for a description of how the Tibion Bionic Leg and ReJoyce Hand and Arm Rehabilitation system have benefited patients in Singapore.

“Stroke is one of the leading factors of morbidity and mortality in Singapore. Due to Singapore’s ageing population, stroke rehabilitation becomes more important now than ever. With conventional stroke rehabilitative therapies, patients perform simple motor tasks repeatedly, which can be monotonous and affect compliance levels. The introduction of new advanced therapies can help stroke patients along their path of recovery in an engaging and progressive manner,” said Philippe Steiner.
Conflicting reports highlight scientific data gaps in Sri Lanka’s chronic kidney disease

A WHO study that blames arsenic for rising levels of chronic kidney disease in Sri Lanka is in conflict with another study that points to poor quality drinking water, report Dilrukshi Handunnetti and Smriti Daniel.

The clashing claims on the causes of chronic kidney disease (CKD) and the absence of scientific data highlight a need for capacity building in disease surveillance and data gathering, experts say.

CKD involves progressive kidney damage and loss of the organ’s function of excreting waste products over three or more months. The absence of clinical symptoms until late stages makes diagnosis and treatment difficult.

Sri Lanka has reported a spurt in CKD cases since the 1990s with 80 percent of patients ending up with total kidney failure within two years of diagnosis. Treatment – dialysis or organ transplantation – being costly, death becomes inevitable for most victims.

The WHO study – commissioned by Sri Lanka’s ministry of health and released to the media on 15 August – attributed CKD to arsenic in groundwater. It called for a robust regulatory framework “to improve the quality control of imported fertiliser(s), particularly with regard to nephro-toxic (kidney damaging) agents such as cadmium and arsenic.”

A day later, the New Delhi-based non-government organisation (NGO) Centre for Science and Environment (CSE) released a separate report on CKD, with conflicting conclusions.

Commissioned by Sri Lanka’s ministry of water supply and drainage and a local NGO, Centre for Environmental Justice, the CSE study ruled out arsenic or heavy metals such as cadmium, lead and chromium in food and water as the cause of CKD, and pointed, instead, to poor water quality.

Tests by the CSE revealed dissolved solids, hardness, calcium and alkalinity exceeding desirable levels in water drawn from dug wells or tube wells and used unfiltered by people in affected areas.

The CSE findings were released in Anuradhapura in Sri Lanka’s North-Central province which, along with the city of Polonnaruwa, has high CKD prevalence.

CSE’s findings are yet to be peer-reviewed. Sri Lanka’s minister for water supply and drainage has accepted them. “We are planning to launch mobile drinking water services and also establish rural water schemes with treatment of water,” Dinesh Gunawardene told SciDev.Net.

The CSE found CKD cases to be typically of men in the 30–60 age group who were paddy farmers or agricultural labourers living in Sri Lanka’s dry zone. In recent years, however, the disease has spread into the North-Western, Eastern, Central, Northern and Uva provinces and has begun to claim women, children and even cattle as victims.

CSE’s pollution monitoring laboratory analysed 35 water samples from key affected areas and compared them with non-affected areas. It also tested 16 soil samples, six rice plant and grain samples, five pesticide samples and three fertiliser samples for arsenic content.

While WHO placed the figure of those affected by CKD at 400,000 people, the CSE said the figure was closer to 15,000.

Chandra Bushan, deputy director-general at CSE, said the focus of research should now switch to the possible role of toxins and heavy metals from sources other than food and drinking water, particularly water with high content of calcium, fluorides and total dissolved solids.

Oliver Illeperuma, head of the department of chemistry at the Peradeniya University, told SciDev.Net that the divergent opinions expressed by the two teams underscored the need for better data gathering.

“Sound data gathering becomes possible with scientific capacity building. That will also lead to scientifically-sound decision-making on long- and short-term measures required to tackle the spread of the disease,” Illeperuma said.

Priyani Paranagama, head of the chemistry department at Kelaniya University, said her team’s independent research, which has not been peer-reviewed, has indicated traces of arsenic in the unnaturally dark soles and palms of patients.

Some autopsies of CKD victims, conducted by the health ministry over the past two years and whose reports were analysed by a WHO team, have established retention of arsenic in hair and nails, Paranagama told SciDev.Net.

Paranagama said the next phase of WHO research on behalf of the health ministry would focus on “how to clear the soil of arsenic residue.”

Source: SciDev
InDex Pharmaceuticals announced the filing of a new patent with the United States Patent and Trademark Office and with the European Patent Office. The company thereby continues to strengthen the company's intellectual property portfolio around its lead drug candidate Kappaproct. The newly filed patent with the title "Methods for prevention of colectomy" covers methods for preventing or reducing the need of colectomy using an oligonucleotide with a specific core sequence and has the potential to extend patent protection on Kappaproct to 2032. Kappaproct is a DNA-based synthetic oligonucleotide, which functions as an immunomodulatory agent by targeting TLR9.

Kappaproct is currently in a phase III study in Europe for the treatment of chronic, active, treatment-refractory ulcerative colitis. InDex Pharmaceuticals already holds broad patent protection for Kappaproct for the treatment of steroid-resistant inflammatory diseases in both Europe and the US through at least 2027, with the possibility of a 3 to 5-year term extension after market approval.

"With our patent portfolio, we already have very solid protection for Kappaproct and this newly filed patent will even further broaden and strengthen our global intellectual property position," said Jesper Wiklund, CEO of InDex Pharmaceuticals.

"There is a significant unmet medical need for patients with gastrointestinal disease, who have tried all available therapies and whose only remaining option is highly invasive surgery. Successful treatment with Kappaproct would enable patients to avoid surgery and dramatically improve the lives and prospects of these very ill individuals."

In June 2012, InDex Pharmaceuticals reported positive data from the Company's compassionate use program with its lead compound Kappaproct. The findings published in the peer-reviewed journal Inflammatory Bowel Diseases showed that more than two years post treatment, all but one of the treated patients had avoided the need for colectomy, with the longest patient being in symptom-free remission for over 27 months.
Novozymes, the world leader in bioinnovation and industrial enzymes, and Terranol, a Denmark-based biotechnology company specialized in yeast, announced an agreement that will ensure the final optimization of the Terranol C5 yeast strain and give Novozymes the rights to register and market Terranol’s C5 yeast technology. C5 yeast is an essential component in the production of cellulosic ethanol, and the partnership will allow Novozymes to speed up global rollout of Terranol’s yeast to customers in the cellulosic ethanol industry. Wide availability of a high-performing and cost-efficient yeast will enable the nascent industry to fast-track the transition from demonstration-scale production to large-scale commercialization.

“With our combined R&D capabilities we can ensure the final optimization of the strain in order to achieve maximum economic performance for our cellulosic ethanol customers,” says Claus Crone Fuglsang, Vice President R&D at Novozymes. Advanced biofuels are approaching large-scale commercialization, but various steps in the production process can still be improved to make production cheaper and more efficient. When producing cellulosic ethanol, enzymes convert cellulose and hemicellulose in biomass such as corn stover and wheat straw to sugars, which are then fermented into ethanol. To obtain optimal yields it is important to ferment not only the easily accessible C6 sugars (glucose), but also the more difficult C5 sugars (xylose and arabinose).

“A yeast that ferments C5 sugars is essential to cost-efficient production of cellulosic ethanol,” says Birgitte Rønnow, CEO of Terranol. “Our C5 yeast is among the furthest developed in the industry and by leveraging Novozymes’ global marketing muscle we can speed up its commercialization.”

In February, Novozymes launched Novozymes Cellic® CTec3, the best-performing enzyme on the market for production of cellulosic ethanol. The first commercial-scale cellulosic ethanol plants are scheduled to open later this year.

Partners aim to accelerate the development of C5 yeast to ensure fast commercialization of advanced biofuels made from agricultural waste, energy crops and other types of biomass.
The end of July 2012 proved exciting for the world of biosimilar manufacturers. However, for the regulatory officials worldwide it meant more uncertainty and unknowns about proper, global biosimilar guidelines. On July 23, 2012, South Korean biosimilar manufacturer Celltrion announced the approval of Remsima (CT-P13), a biosimilar antibody, by the Korean Food and Drug Administration. Remsima is a biosimilar version of Johnson & Johnson’s Remicade (infliximab) which was one of the first monoclonal antibody TNF inhibitors approved for the treatment of Rheumatoid Arthritis (RA). Remsima is approved for several indications and will be marketed in Asia and South America by the end of the year. In Europe, Celltrion filed for market authorization with partner Hospira to launch Remsima under the name of Inflectra. Interestingly, Remsima is only the first officially approved biosimilar antibody for RA therapy as Reditux, a MabThera biosimilar, was launched in India in 2007, but under unapproved biosimilar development guidelines. The first-ever approved biosimilar, Omnitrope (somatropin), arrived on the European market in 2006. Since then 14 more drugs across the drug classes of human growth hormone, granulocyte stimulating factor, and erythropoietin have been approved in the European Union (EU).

The definition of a biosimilar drug according to the World Health Organization is as follows: a biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product. This definition seems straightforward, but guidelines to maintain the safety and efficacy of these drugs have been difficult to draft and approve worldwide. The issues which have come under scrutiny include questioning of the biosimilar formulation, the amount of clinical trial data needed, and quality control of manufacturing practices. Without a global resolve and understanding of the clinical and regulatory factors involved in designing and marketing a biosimilar drug, the market uptake will likely be slow.

With several antibodies coming off patent in the next few years, biosimilars will be waiting in the wings to take some revenue, but they are not likely to cannibalize the market due to the uncertainties which have been in question. Even though the biosimilar market earned about $170m in 2010, uptake will be slow compared to generics for reasons stated, while considerable investment is also needed to produce a biosimilar and bring it to market. In order for biosimilars to become competitive, price reduction strategies could likely grab the attention from consumers, physicians, and payers, which could increase the biosimilar market share. However, due to high manufacturing costs, biosimilar drugs are less likely to be included in discount offerings which generic drugs are accustomed to.

Since the upcoming biosimilars are from different drug classes than those currently on the market, there will be supply and demand drivers. Companies will be trying to get the leg-up on cost-saving strategies and maximize their potential to lead in quality assurance of the production of biosimilars. Pharmaceutical and generic manufacturers are entering this arena, and some are being guided by Contract Research Organizations (CROs) to aid in market strategy specific to biosimilars. Big Pharma companies such as Amgen, Biogen Idec, and Merck are competing with well-known generics companies which include Hospira, Teva, and Watson. The CRO guidance is coming from familiar organizations such as Biocon, Harvest Moon, and Quintiles. Other potential players looking for a piece of the biosimilar pie include Astra Zeneca, Fujifilm, and GE Healthcare.

In 2011, the US was responsible for 36% of the worldwide biologic drug sales, while the five major European markets collectively took second with 22%. Currently, it is estimated that the biosimilar market will reach close to $4 billion by 2017. The US is lagging behind with legislation and regulations for the approval and marketing of biosimilars as compared to the EU, Japan, and numerous other developed countries that have had terms in place for several years. GlobalData believes that, if the US healthcare system and US FDA are unable to design and approve regulatory guidelines for biosimilar drugs within the next few years, the US healthcare system will lose more money, and be forced to pay for more expensive brands.
Researchers asked people to read Jane Austen in an MRI machine, and say the surprising results suggest reading closely could be "training" for our brains.

Neurobiological experts, radiologists, and humanities scholars are working together to explore the relationship between reading, attention, and distraction—by reading Jane Austen.

Surprising preliminary results reveal a dramatic and unexpected increase in blood flow to regions of the brain beyond those responsible for "executive function," areas which would normally be associated with paying close attention to a task, such as reading, says Natalie Phillips, the literary scholar leading the project.

During a series of ongoing experiments, functional magnetic resonance images track blood flow in the brains of subjects as they read excerpts of a Jane Austen novel. Experiment participants are first asked to skim a passage leisurely as they might do in a bookstore, and then to read more closely, as they would while studying for an exam.

Phillips says the global increase in blood flow during close reading suggests that "paying attention to literary texts requires the coordination of multiple complex cognitive functions." Blood flow also increased during pleasure reading, but in different areas of the brain. Phillips suggests that each style of reading may create distinct patterns in the brain that are "far more complex than just work and play."

The experiment focuses on literary attention, or more specifically, the cognitive dynamics of the different kinds of focus we bring to reading. This experiment grew out of Phillips' ongoing research about Enlightenment writers who were concerned about issues of attention span, or what they called "wandering attention."

Phillips, who received her PhD in English literature at Stanford in 2010, is now an assistant professor of English at Michigan State University. She says one of the primary goals of the research is to investigate the value of studying literature.

Beyond producing good writers and thinkers, she is interested in "how this training engages the brain."

The research is "one of the first fMRI experiments to study how our brains respond to literature," Phillips says, as well as the first to consider "how cognition is shaped not just by what we read, but how we read it."

Critical reading of humanities-oriented texts are recognized for fostering analytical thought, but if such results hold across subjects, Phillips says it would suggest "it's not only what we read—but thinking rigorously about it that's of value, and that literary study provides a truly valuable exercise of people's brains."

Though modern life's cascade of beeps and buzzes certainly prompts a new kind of distraction, Phillips warns against "adopting a kind of historical nostalgia, or assuming those of the 18th century were less distracted than we are today."

Many Enlightenment writers, Phillips notes, were concerned about how distracted readers were becoming "amidst the print-overload of 18th-century England."

Rather than seeing the change from the 18th century to today as a historical progression toward increasing distraction, Phillips likes to think of attention in terms of "changing environmental, cultural, and cognitive contexts: what someone's used to, what they're trying to pay attention to, where, how, when, for how long, etc."

Ironically, the project was born out of a moment of distraction. While sitting on a discussion panel (which happened to be one of the first on cognitive approaches to literature), Phillips found herself distracted from the talk by the audience's varieties of inattention: "One man was chatting to his neighbor; another person was editing their talk; one guy was looking vaguely out the window; a final had fallen asleep."

The talk inspired Phillips to consider connections between her traditional study of 18th-century literature and a neuroscientific approach to literary analysis.

Phillips was especially intrigued by the concept of cognitive flexibility, which she defines as "the ability to focus deeply on one's disciplinary specialty, while also having the capacity to pay attention to many things at once," such as connections between literature, history of mind, philosophy, neuroscience, and so on.

Samantha Holdsworth, a research scientist specializing in MRI techniques, recalls an early conversation about the project when two scientists were trying to communicate with three literary scholars: "We were all interested, but working at the edge of our capacity just to understand even 10 percent of what each other were saying."

After working through the challenges of disciplinary lingo, the team devised a truly interdisciplinary experiment. Participants read a full chapter from Mansfield Park, which is projected onto a mirror inside an MRI scanner. Together with a verbal cue, color-coding on the text signals participants...
to move between two styles of attention: reading for pleasure or reading with a heightened attention to literary form.

The use of the fMRI allows for a dynamic picture of blood flow in the brain, “basically, where neurons are firing, and when,” says Phillips. Eye-tracking compatible with fMRI shows how people’s eyes move as they read. As Phillips explains, the micro-jumps of the eyes “can be aligned with the temporal blood flow to different regions in the brain.”

When participants are done with a chapter, they leave the scanner and write a short literary essay on the sections they analyzed closely. The test subjects, all literary PhD candidates from the Bay Area, were chosen because Phillips felt they could easily alternate between close reading and pleasure reading.

After reviewing early scans, neuroscientist Bob Doherty, director of the Stanford Center for Cognitive and Neurobiological Imaging (CNI), says he was impressed by “how the right patterns of ink on a page can create vivid mental imagery and instill powerful emotions.”

Doherty was also surprised to see how “a simple request to the participants to change their literary attention can have such a big impact on the pattern of activity during reading.”

The researchers expected to see pleasure centers activating for the relaxed reading and hypothesized that close reading, as a form of heightened attention, would create more neural activity than pleasure reading.

If the ongoing analysis continues to support the initial theory, Phillips says, teaching close reading (i.e., attention to literary form) “could serve—quite literally—as a kind of cognitive training, teaching us to modulate our concentration and use new brain regions as we move flexibly between modes of focus.”

With the field of literary neuroscience in its infancy, Phillips says this project is helping to demonstrate the potential that neuroscientific tools have to “give us a bigger, richer picture of how our minds engage with art—or, in our case, of the complex experience we know as literary reading.”

Source: Futurity
The U.S. Department of Agriculture (USDA) announced a $99 million partnership with Chemtex to support construction of a new advanced biofuels plant in the United States. The plant is expected to be located in Sampson County, North Carolina and produce 20 million gallons per year from energy crops. Construction is targeted to begin in late 2012.

"Novozymes is excited to partner with Chemtex to convert energy crops into cellulosic ethanol in North Carolina. It is a great step forward for the U.S. biofuels industry and an endorsement of the technologies Chemtex and Novozymes have each developed. I am confident our collaboration will become a benchmark for the advanced biofuels industry in the U.S.,” said Peder Holk Nielsen, Executive Vice President, Novozymes.

Slated to open in 2014, the plant will employ approximately 65 employees and indirectly generate 250 more jobs in the community, not including construction jobs. The feedstock will be grown on low productivity/marginal land that is in part being utilized as “spray fields” for the hog farming industry.

Chemtex will use Beta Renewables’ PROESA® technology to produce cost-competitive ethanol using energy grasses and agricultural waste as its feedstock. PROESA is the same technology that will be used at the world’s first commercial-scale cellulosic biofuel plant in Crescentino, Italy, expected to start operations in the fall of 2012, and also in a series of plants to be built by GraalBio in Brazil. Novozymes is the enzyme partner for the three announced ethanol plants running on PROESA (Crescentino, GraalBio and Chemtex.)

"Realizing a commercial scale cellulosic ethanol plant in the United States and proving that it can produce competitive sustainable ethanol is an important milestone in the commercialization process of advanced biofuels,” said Guido Ghisolfi, President of The Chemtex Group. “Our collaboration with Novozymes is an important aspect of this project and further validates what can be achieved when industry-leading players and technologies join forces. We believe that the plant can become a model for future cellulosic ethanol production in America, providing jobs and benefiting local economies and U.S. energy security."

The support announced follows a commitment of $3.9 million from USDA’s Biomass Crop Assistance Program (BCAP) to Chemtex in June 2012. Funds from the BCAP award helped establish and grow more than 4,000 acres of feedstock, such as switchgrass and miscanthus, used to make cellulosic ethanol.

Almost two-thirds of future Renewable Fuel Standard volumes are allocated for advanced biofuels like the cellulosic ethanol from Chemtex. To date, the U.S. biofuels industry has created 400,000 jobs. Advanced biofuels coming online are expected to create an additional 800,000 by 2022.

As part of the Biofuels Leadership Coalition, Novozymes and its partners have invested one billion dollars in bringing advanced biofuels technologies to market and creating associated jobs.

Cellulosic ethanol is produced from biomass such as wheat straw, corn stover, sugarcane bagasse, municipal waste, or energy crops, which is first broken down into a pulp. Enzymes are then added, turning the pulp into sugar which is fermented into ethanol. Novozymes is the world’s leading provider of enzymes to the biofuels industry.
Fossil fuel and renewable energy subsidies on the rise

Total subsidies for renewable energy stood at $66 billion in 2010, but are still dwarfed by the total value of global fossil fuel subsidies estimated at between $775 billion and more than $1 trillion in 2012, according to new research conducted by the Worldwatch Institute for its Vital Signs Online service. Although the total subsidies for renewable energy are significantly lower than those for fossil fuels, they are higher per kilowatt-hour if externalities are not included in the calculations, write report authors from Worldwatch's Climate and Energy team.

Estimates based on 2009 energy production numbers placed renewable energy subsidies between 1.7¢ and 15¢ per kilowatt-hour (kWh), while subsidies for fossil fuels were estimated at around 0.1-0.7¢ per kWh. Unit subsidy costs for renewables are expected to decrease as technologies become more efficient and the prices of wholesale electricity and transport fuels rise.

The production and consumption of fossil fuels add costs to society in the form of detrimental impacts on resource availability, the environment, and human health. The U.S. National Academy of Sciences estimates that fossil fuel subsidies cost the United States $120 billion in pollution and related health care costs every year. But these costs are not reflected in fossil fuel prices.

"These so-called hidden costs, or externalities, are in fact very real costs to our societies that are not picked up by the polluter and beneficiary of production but by all taxpayers," said Alexander Ochs, Director of Worldwatch's Climate and Energy program and report co-author. "Local pollutants from the burning of fossil fuels kill thousands in the U.S. alone each year, and society makes them cheaper to continue down their destructive path."

Shifting official support from fossil fuels to renewables is essential for decarbonizing the global energy system. Such a shift could help create a triple win for national economies by reducing global greenhouse gas emissions, generating long term economic growth, and reducing dependence on energy imports.

According to projections by the International Energy Agency (IEA), if fossil fuel subsidies were phased out by 2020, global energy consumption would be reduced by 3.9 percent that year compared with having subsidy rates unchanged. Oil demand would be reduced by 3.7 million barrels per day, natural gas demand would be cut by 330 billion cubic meters, and coal demand would drop by 230 million tons of coal. And the effects of the subsidy removal would extend beyond the end of the phaseout period. By 2035, oil demand would decrease by 4 percent, natural gas by 9.9 percent, and coal demand by 5.3 percent, compared with the baseline projection.

Overall, carbon dioxide emissions would be reduced by 4.7 percent in 2020 and 5.8 percent in 2035. The IEA's chief economist recently estimated that eliminating all subsidies in 2012 for coal, gas, and oil could save as much as Germany's annual greenhouse gas emissions each year by 2015, while the emission savings over the next decade might be enough to cover half of the carbon savings needed to stop dangerous levels of climate change.

"At the same time, a phase-out of fossil fuel subsidies would level the playing field for renewables and allow us to reduce support for clean energy sources as well," said Ochs. "After all, fossil fuels have benefited from massive governmental backing worldwide for hundreds of years."

Progress toward a complete phaseout, however, has been minimal. The 2009 pledge by the Group of 20 major economies to reduce "inefficient fossil fuel subsidies" has been left vague and unfulfilled. The lack of a definition has left countries to make their own determination if their subsidies are inefficient. As of August 2012, G20 countries had not taken any substantial action in response to the pledge—six members opted out of reporting altogether (an increase from two in 2010), and no country has yet initiated a subsidy reform in response to the pledge. Furthermore, there continues to be a large gap between self-reported statistics and independent estimates in some countries.

Some argue that reducing subsidies would disproportionately affect the poor. An IEA survey of 11 developing and emerging countries, however, found that only 2-11 percent of subsidies went to the poorest 20 percent of the population, showing that subsidies tend to be regressive.

Fossil fuel subsidies continue to far outweigh support for renewable energy. Although independent reporting on these subsidies has increased, global efforts to move forward with subsidy reform have been hindered by a variety of causes, leaving international pledges unfulfilled.
Traditional Chinese medicine is generally treated with skepticism by medical professionals outside China. Now, scientists in China and the United States have enlisted the help of biotechnology to show that drugs used in it have legitimate science-based value, and represent an untapped source of treatments.

“There are around 100,000 formulas going back 2000 years, drugs that can be used to treat a range of illnesses, from depression to osteoporosis,” says Karl Wah-Keung Tsim from Hong Kong’s University of Science and Technology, quoted in an article in the Bulletin of the World Health Organisation.

Traditional medicine represents around 40 per cent of China’s pharmaceutical market, with an annual turnover of US$21 billion. The government says its support for the industry is increasing rapidly: last year it invested around US$1 billion in traditional medicine research and projects — almost three times the amount provided in 2010 — according to China’s deputy health minister, Wang Guoqiang.

But few drugs or techniques from China’s ancient texts and traditional culture have been incorporated into mainstream medical practice outside the country, where attitudes towards Chinese medicine remain largely characterized by suspicion, due to the lack of evidence supporting its medicinal value, as well as concerns about product quality.

In May 2011, for example, the European Union controversially banned the sale of traditional Chinese herbal treatments not registered under the EU Traditional Herbal Medicines Registration Scheme.

Chinese scientists, with support from the US National Institutes of Health, are now seeking to change this. They are using contemporary technology to improve drug quality standards and convince the international research community that traditional Chinese medicine has a solid evidential basis.

Biotechnology unveils secrets of Chinese medicine

Researchers have been trying to isolate the active ingredients in traditional medicines - a challenging task due to the complicated molecular structure of many herbal compounds.

Yung H Wong, director of the life sciences division at the Biotechnology Research Institute in Hong Kong, says that biotechnology holds the key to unraveling this complexity.

Wong and his team use high-throughput screening platforms to assess the individual molecular activity and properties of large collections of drug extracts and compounds.

But it is the complexity of the interactions between the different components of herbal compounds, rather than their individual properties, what makes the compounds so effective, says Yung-Chi Cheng, an oncology researcher at Yale University, in the United States.

“By focusing on the single components we miss the big picture,” Cheng said. Individually, the medicines’ mechanisms “was not that potent”; but “working together makes a significant difference”.

Cheng has no doubts about the value of Chinese medicine. “Traditional Chinese medicine is a human treasure, and it should be shared with the world,” he said.

Source: Bulletin of the World Health Organization
Climate change a mixed blessing for wheat, say experts

Climate change may have a profound effect on the world’s ability to produce wheat — one of its staple crops — and adaptation efforts must take into account both the positive and negative effects of climate shifts, say wheat experts.

Production in some regions, such as India and Mexico, is predicted to be negatively affected by climate change, according to Thomas Lumpkin, director general of the International Maize and Wheat Improvement Center (CIMMYT).

But, in other regions, such as northern China, production may benefit from warmer winters.

“Both high temperatures and reduced rainfall will be more common, and wheat will be the most severely affected major crop,” Lumpkin told SciDev.Net on the sidelines of the 2012 Borlaug Global Rust Initiative (BGRI) Technical Workshop in China this month (1–4 September).

Despite several years of record South Asian harvests, global weather patterns appear to be changing, and regional food shortages may cause political upheaval, Lumpkin said.

Bangladesh has seen its wheat production area and yields reduce dramatically, as a consequence of a heat stress caused by climate change, and the current US drought has led to rising food prices, likely to stir up social unrest, according to Lumpkin.

“We already have evidence that high wheat prices in 2008 helped stimulate the ‘Arab Spring’ events in Libya, Egypt and Syria,” Lumpkin said.

Ravi Prakash Singh, head of CIMMYT’s Irrigated Bread Wheat Improvement and Rust Research programme, agreed: “Each country will need to invest more in agriculture, otherwise food shortages can lead to social unrest, as seen in recent years in some countries”.

Singh told SciDev.Net that climate change has already had both positive and negative effects on wheat production.

“For example, the 2011–12 South Asian wheat season was very favourable, and record wheat production occurred, to the extent [that there were] severe shortages of gunny bags for storing and transporting wheat in India,” Singh said. Such storage shortages were a big problem for the government, and it is likely a large quantity of wheat will be wasted, he added.

In contrast, this year, a delay and reduction in Indian monsoon rains has affected crops severely in rain-fed agricultural areas in South Asia.

Meanwhile, in China, warmer winter temperatures have enabled farmers in some areas to replace spring wheat with winter wheat.

“Warmer temperatures permit longer growing seasons and more crop productivity in northern China if irrigation and rainwater are available,” Lumpkin said. “However, in some areas water use is already higher than sustainable,” he added.

Similarly, in southwestern China, warmer temperatures have extended growing seasons.

But these benefits may be offset by other impacts resulting from climate change, such as an increase in crop disease, scientists have warned.

“Diseases such as stripe rust, leaf and stem rust, fusarium head blight, and powdery mildew will be more severe,” Yuchun Zou, a senior wheat breeder of Crop Research Institute of Sichuan Academy of Agricultural Sciences told SciDev.Net.

Climate change will also bring more drought, he said, adding that breeding efforts should be aimed at adapting new wheat varieties to the impacts of climate change.

“To combat the effects of climate change we need integrated strategies,” Singh said. These include “the development of high-yielding varieties that have more tolerance to drought and heat, but, at the same time, increased investment in grain storage infrastructure and more efficient irrigation systems to utilise water”.

Li Jiao

Source: SciDev.Net
NTOU identified germ cells and somatic cells in coral bodies for the first time in the world

In an NSC press conference on August 29, National Taiwan Ocean University (NTOU) presented the findings of a research team led by the university’s president Ching-Fong CHANG on coral development and reproduction. The research result contributed by the team took the lead in the world unveiling the mechanism of sexual reproduction of scleractinian coral, the understanding of which has opened a heavy door to factitious establishment of coral populations. First of all, the team for the first time in the world found an identifiable marker gene that can help distinguish germ cells and somatic cells in coral bodies, following which, moreover, the team succeeded in developing an antibody and a method to ascertain the early germ cells and the specific location of coral development during both of the breeding season and the non-breeding season. The findings yield better understanding about the cell development of coral bodies, and the research report has been published in the July 27 issue of PLoS One.

The so-called rain forest of the ocean, coral reefs are underwater structures made from calcium carbonate secreted by corals and consist of many polyps that cluster in groups. In response to the decreasing coral coverage, Taiwan tried to restore the corals for a few decades. The main means of restoration are inefficient clonal fragmentation and annual sexual reproduction.

As the result of evolution, coral bodies have no distinct organs and the somatic cells and the germ cells are intermingled together, so we cannot obtain the information about the germ cells and their distribution in coral bodies by separating it from somatic cells via traditional histological analysis. According to Ching-Fong CHANG, vasa gene, which determines germ cells, is widely used as marker gene for germ cells in both vertebrates and invertebrates, which means as long as the vasa gene can be identified; the location of the germ cells can be ascertained.

The research team first collected the information about the germ cells in coral bodies by means of biopsy and immunohistochemistry. Then the team succeeded in selecting and colonizing the vasa gene of coral germ cells, producing an antibody, and locating the specific venue of germ cells’ development. This was a significant breakthrough in the studies of corals, which do not have sexual organs.

Besides, the team also found for the first time that the early germ cells exist in the whole reproduction cycle and they continue the reproduction in turn once they are stimulated by certain signals. CHANG said, this discovery is not easy, for corals do not have sex organs. He continued, the findings bring forth much understanding about the reproduction mechanism of corals and they points out several promising directions and possible methods to activate the development of coral germ cells.

CHANG said, in the future the team will try to specify the factors or hormones relating to the development of coral germ cells. The goal is to develop methods for artificial coral propagation. If the development hormones are identified, the methods to accelerate the development of coral germ cells or to promote the emission of sperms and ova may be developed. This will largely benefit the restoration of coral reefs.
A group of twelve researchers from Taiwan, Malaysia and Australia, including several members of Academia Sinica’s Biodiversity Research Center have found that over the past 26 years the composition of the coral reefs off Kenting in South Taiwan has changed, and their biodiversity has declined. Their findings were published online in the scholarly journal PLoS One.

The researchers found that the coral reefs have been affected by six typhoons and two coral bleaching events over the past 26 years. Corals from the genera Acropora and Montipora have almost disappeared from the reefs, whereas corals belonging to genera Favia and Heliopora have maintained their presence at steady levels. Massive corals such as Porites have increased in abundance, whereas, hard coral species in particular have declined in abundance to less than half over the last quarter of a century, indicating that the health of the coral reefs is in jeopardy and diverse reef assemblage is declining.

The analysis of the changes in the coral communities as well as local ecological disturbances used data obtained from the Wanlitung Reef, which is located on the west coast of the Hengchun Peninsula in Kenting National Park between 1985 and 2012. Results confirmed a change in the composition of the coral communities over time from branching corals to massive corals species. Moreover the total hard coral coverage rate, which was 47.5% in 1985, had gone down to 17.7% in 2010, reducing hard coral cover in the area by 63%. In contrast, macro algae on the reefs and those corals resistant to disturbance increased from 11.3% in 2003 to 28.5% in 2010. These results show that the coral reefs in Taiwan have become less ecologically diverse may not be resilient to repeated major ecological disturbances arising from environmental changes and increased human activity.

Dr. Allen Chen, a research fellow at the Biodiversity Research Center who led the team warned that the coral reef ecosystem provides important habitats for many highly diverse marine organisms. In addition, in 2003 the annual net income provided by coral reefs globally (net benefit per year) was estimated to be up to NT$1 trillion (about US$ 29.8 billion), with an approximate 500 million people worldwide (approximately 7% per cent of all mankind) estimated to live within 100 km of a coral reef. Thus, disruption to the coral reef ecosystem is a major concern to the sustainable development of human society.

Dr. Chen believes, however, that in the face of environmental climate change, long-term ecological research on coral reefs will become increasingly important. For example, the results of the long-term analysis presented in the present study have made clear that since 1996 the reef in Kenting has been in decline as a result of multiple typhoons, particularly typhoon Morakot in 2008, and global sea-surface temperature related worldwide coral bleaching in 1998. Interestingly, a six year period between 1999 and 2005, during which there were no major disturbances, allowed coral cover to return to 1987 levels.

Dr. Chen predicts that recent increases in the occurrences of typhoons along the coastline of Taiwan (Kenting, Orchid Island and Green Island) will likely increase the irreversible damage to the coral reefs and related diversity of coral communities, which in turn may impact local fisheries and the sustainable development of the tourism industry. He emphasizes that, long-term ecological research, and scientific data collection and analysis as well as moves by the Taiwan government to design suitable marine conservation policies and provide information are needed to prevent the coral reef ecosystem from the consequences climate change and human activities.
A National Cheng Kung University (NCKU) research team has discovered Near-Infrared Light-Responsive oligonucleotide-gated Au nanoensembles (Au nanorod complex), a potent new anti-cancer complex that is seen as a promising targeted therapy for curing cancer.

This medical discovery was selected as an important and urgent paper, becoming the image of back cover in the July 2012 issue of Advanced Materials, and has drawn big attention in the academic world and the biotechnology industry as well.

The team, led by Chen-Sheng YEH, NCKU Distinguished Professor of Department of Chemistry, focused on the development of NIR light-responsive oligonucleotide-gated Au nanoensembles (Au nanorod complex) for cancer therapy and the result proved that Au nanorod complex could provide better efficiency of cancer therapy by reducing the cancer survival rates by 30%.

Au nanorod complex provides a new platform for cancer therapy, a platform which, depending on different diseases, encapsulates different drugs and small interfering RNA (siRNA) which has special functions to achieve chemotherapy and gene therapy, according to Professor YEH.

Professor YEH pointed out that the surface of Au nanorod complex coated with silica can encapsulate anti-cancer drugs.

To avoid the loss of anti-cancer drugs from Au nanorod complex during the delivery process and reduce side effects of anti-cancer drugs, the double-stranded DNA (dsDNA) as a net in covering the surface pores was used to conjugate on the surface pores of silica.

When Au nanorod complex was irradiated with NIR light, Au nanorods absorbed NIR light and were transferred to heat.

The generated heat transferred from Au nanorods to outside dsDNA induced dehybridization of the dsDNA as the net was destroyed by heat. After dehybridization of dsDNA, the encapsulated drugs were released from mesopores to outside and killed cancer cells.

Experimental results show that cancer survival rate can be reduced from 80% to about 50%, confirming the gold nanorods pharmaceutical compound has achieved good therapeutic effect.

The advantage of using NIR light to trigger drug release was that NIR was the biological window, where both blood and soft tissues transmission is optimal due to low energy absorption, providing maximum penetration. Therefore, the developed Au nanorod complex has triggered drug release, maximizing the therapeutic properties of both chemotherapy and gene therapy.

Moreover, the design of the treatment which can be tailored by the medical needs to load the appropriate drug treatment is believed to be a very curative treatment platform, according to YEH.

YEH's team has applied for patent in Taiwan and the United States, and will continue to conduct animal testing and human trials.
Chinese scientists successfully crack the genome of diploid cotton

The international research team led by Chinese Academy of Agricultural Sciences and BGI has completed the genome sequence and analysis of a diploid cotton — *Gossypium raimondii*. The cotton genome provides an invaluable resource for the study and genetic improvement of cotton quality and output, and sheds new lights on understanding the genetic characteristics and evolutionary mechanism underlying cotton and its close relatives. The study was published online in Nature Genetics.

Cotton, also known as “white gold”, is an important cash crop worldwide. Its fiber is one of the oldest fibers under human cultivation, which traces over 7,000 years old recovered from archaeological sites. The cotton production provides income for approximately 100 million families, and approximately 150 countries are involved in cotton import and export. Additionally, in scientific research, cotton also serves as an excellent model system for studying polyploidization, cell elongation and cell wall biosynthesis.

In this study, researchers sequenced the genome of *G. raimondii* by the next-generation sequencing technology, yielding a draft cotton genome with 103.6-fold genome coverage. Over 73% of the assembled sequences were anchored on 13 *G. raimondii* chromosomes. They identified 2,355 syntenic blocks in the *G. raimondii* genome, and found that approximately 40% of the paralogous genes were present in more than 1 block, which suggests that this cotton genome has undergone substantial chromosome rearrangement during its evolution.

Through comprehensive comparison and analysis, researchers observed that one paleohexaploidization event occurred in the *G. raimondii* genome at approximately 130.8 million years ago, while the event is commonly found in eudicots. They also found the evidence to support a cotton-specific whole-genome duplication event occurred at approximately 13–20 million years ago.

Cotton is known to produce a unique group of terpenoids such as gossypol. The accumulated gossypol and related sesquiterpenoids produced by cotton in pigment glands can be as a resistance against pathogens and herbivores. The majority of cotton sesquiterpenoids are derived from a common precursor which is synthesized by (+)-δ-cadinene synthase (CDN) in gossypol biosynthesis. Through the phylogenetic analysis on *G. raimondii* and eight other sequenced plant genomes, they found that the cotton, and probably Theobroma cacao, were the only sequenced plant species that possess an authentic CDN1 gene family for gossypol biosynthesis.

Furthermore, the transcriptomic comparison between the fiber-bearing *G. hirsutum* and the non-fibered *G. raimondii* demonstrated that three synthases are important for cotton fiber development, including sucrose synthase (Sus), 3-ketoacyl-CoA synthase (KCS) and 1-aminoacyclopropane-1-carboxylic acid oxidase (ACO). Meanwhile, the MYB and bHLH transcription factors preferentially expressed in fiber may be useful to explain the molecular mechanisms that are in charge of governing fiber initiation and early cell growth.

Zhiwen Wang, Project Manager at BGI, said, “The completed *G. raimondii* genome provides a good reference for accelerating the genomic research on tetraploid cotton species such as *G. hirsutum* and *G. barbadense*. It also will lay a solid foundation for researchers to further boost cotton quality and productivity by comprehensively exploring the genetic mechanisms underlying cotton fiber initiation, gossypol biosynthesis and resistance against pathogens and herbivores.”
Although a challenge for the national government, a growing aging population combined with the country's universal healthcare system means that Taiwan's healthcare market can expect to expand in the future, says the latest report by industry experts GlobalData.

According to the latest study, Taiwan's pharmaceutical industry is predicted to climb from a $3.8 billion valuation in 2011 to $4.8 billion by 2020, while the medical devices industry is expected to reach $3 billion by the end of the decade from a 2011 valuation of $1.9 billion.

GlobalData's report states that the country's aging population will be an important factor in driving this growth, with just under 11% of Taiwan's residents above the age of 65 last year. Taiwan's population increased slightly between 2005 and 2010, from 22.8 million to 23.2 million, but this growth was mainly down to a longer national life expectancy, as the birth rate fell from 9.1 per 1,000 population in 2005 to 7.2 per 1,000 population in 2010.

Taiwan's over-65 population will expand still further, states GlobalData, accounting for 13% of the country's people by 2020. Correspondingly, Taiwan's disease burden is forecast to increase, placing greater strain on the National Health Insurance (NHI) system and its commitment to universal healthcare. According to Taiwan's Department of Health (DoH), healthcare expenditure as a percentage of Gross Domestic Product (GDP) will climb from 6.6% in 2011 to 7.2% by 2020.

However, despite Taiwan's compulsory insurance policy, out-of-pocket expenditure in the country is high, representing 36.4% of total health spending in 2010.

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A research team led by Academician C-K James Shen, a Distinguished Research Fellow at the Institute of Molecular Biology recently found that TAR DNA binding protein 43 (TDP-43) is a likely cause of the development of the motor neuron disease amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease. Using a mouse model, first author Ms. Lien-Szu Wu and colleagues showed that mice with inactivation of the Tardbp gene (the gene that encodes TDP-43 protein) in spinal cord motor neurons exhibited progressive and male-dominant development of ALS-related abnormalities including spine curvature (kyphosis), motor dysfunctions, muscle weakness/atrophy, and motor neuron loss. The study was published in The Journal of Biological Chemistry.

Amyotrophic lateral sclerosis, the most common motor neuron disease, is a progressive, adult-onset degenerative disorder of motor neurons in the primary motor cortex, corticospinal tracts, brainstem and spinal cord, leading to paralysis of the voluntary muscles. Currently, the incidence of ALS is 1–2 per 100,000 worldwide each year and its prevalence is 4–6 per 100,000 of the total population, with a lifetime ALS risk of 1 in 400 to 1 in 1,000. Most incidences of ALS are sporadic (sALS) but approximately 10% of patients have a family history (fALS) of the disease. Mutations in the Tardbp gene have been identified in about 4% of fALS and less than 1% of sALS.

Interestingly, the TDP-43 protein is the major component of the ubiquitinated inclusions (UBIs) in the diseased cells of 80% of ALS patients. TDP-43 has been implicated in a number of cellular activities (such as transcriptional repression and alternative splicing). However, the physiological functions of TDP-43 in normal individuals and whether it causes neurotoxicity through gain-of-function or a loss-of-function in ALS are largely unknown. Currently, there is no effective cure for ALS, thus, suitable mouse models are urgently needed to further understand ALS and the development of drugs for ALS. The characteristics of this ALS mouse model also provide the foundation for design of other ALS mouse model(s).

This study establishes an important role of TDP-43 in the long-term survival and functioning of the mammalian spinal cord motor neurons, and also establishes that loss of TDP-43 function could be one major cause of neurodegeneration in ALS with TDP-43 involvement. This research was supported by the Frontiers of Science Award from the National Science Council and Academia Sinica.
Almost 250 years after Edward Jenner inoculated a young boy with pus from the hand of a milkmaid who had cowpox, vaccines continue to make headlines.

The latest news comes from the US Center for Disease Control and Prevention (CDC) which reports that over 2011-2012, the flu infection rate was about half of that of the previous year. It appears that H1N1 and H3N2 virus circulations have shown low levels of activity and there has been a good match between the vaccines and the circulating strains. It has thus become the accepted practice to administer flu vaccines to children ages six to eight years.

Good news concerning vaccines continue to feature in the popular media, almost but not quite balanced by doom and gloom reports of vaccine-induced disasters accompanied by dire warnings and ongoing controversies. First the good news:

Vaccines improve immunity to particular and specific diseases. The altered form of microorganism that comprises the vaccine stimulates the immune system to recognize the agent as foreign, then to remember it, and finally to destroy it. The process is repeated if and when the immunized person later encounters the unaltered disease-causing microorganism. Vaccines cannot guarantee complete protection from the disease as the immune system in some individuals may not respond adequately or the quality of the vaccine might not be ideal. Nevertheless, their ability to prevent vaccine preventable diseases (VPDs) has been reflected in a 99% drop in polio since 1988, and a 78% decrease in measles deaths in the last decade. Whereas in 1988 there were approximately 350,000 cases of polio worldwide, there are now less than 1,300.

Sadly, it is estimated by the WHO that 8.8 million children under five years of age die each year, mainly in poor countries. This horrific toll could be reduced by 2 million with more widespread use of available vaccines. Such preventable culprits include tetanus, rotavirus, pneumococcus, human papilloma virus, haemophilus influenzae, hepatitis, rubella, encephalitis, cholera, yellow fever and meningococcus. Access to such vaccines requires the establishment of adequate supply, cooperation in reaching targets and of course appropriate financial support.

The bad news, aside from the documented underuse of pneumococcal conjugate, meningococcal and rotavirus vaccines, is the shrill voices that would recommend they not be used at all. The headlines are frequent, repetitive, emotional and persistent. They range from a denial of disease risk, a claim that most diseases are relatively harmless, that there is inadequate research to support any immunity benefit beyond ten years, and the hottest debate of all – Adverse Vaccine Reactions. Cases have been presented of children who exhibited vaccine reactions that resulted in death within hours of receiving a vaccine. Vaccines have been blamed for Sudden Infant Death Syndrome (SIDS), autism, diabetes, brain damage and auto-immune disease. Are these reports merely anecdotes, or are they related to coincidental upsurges in some diseases? Perhaps they relate to vaccines being cultured in monkeys, the introduction of foreign proteins or other excipient chemicals such as stabilizers and antibiotics. Furthermore, there is the troubling issue of herd immunity, in which those in favor of vaccination have the objective of protecting the population as a whole. Some parents choose to make decisions purely for their...
own family; they question and indeed resent ‘sacrificing’ their own children for the good of the community.

The battle lines have now become clearly identified. On one side are the aligned troops comprised of the majority of medical doctors, the pharmaceutical companies and the CDC. Across the divide are some doctors and researchers, many alternative medicine practitioners, some religious groups and most deserving of our respect and concern, parents who are convinced that children have been harmed by vaccines. These parents firmly believe that they are not adequately given the opportunity for informed consent. They quite reasonably dislike being pressured by laws requiring vaccination, school admission requirements and threats of being turned in to Child Protective Services if they neglect their children’s vaccinations. Since society as a whole is only protected if nearly everyone gets the standard vaccines, they must be promoted to the public in a fully honest way. Regrettably, much of the material that parents might access to inform themselves is presented inaccurately or is distorted to the extent of being deceptive. Both the National Vaccine Information Center and CDC give balanced views, albeit opposing ones. Many of us used Robert Mendelson’s “How to raise a Healthy Child” as a good starting point for self education on the vaccine dilemma.

Each side argues passionately and persuasively. How can one ignore such articles as “Many vaccines are expired or improperly stored” from a US Government report, or “Vaccine madness: New mumps jab cultured from dog kidneys linked to canine allergies” blaming an unlicensed vaccine shipped into the UK? A parent can be forgiven for being concerned after reading that "Breast feeding can transmit dangerous vaccine viruses to newborns" in the Canadian Medical Association Journal (CMAJ). In a recent article published in a Natural Health brochure, readers were asked whether most United States citizens would opt out of getting vaccines if they knew that ‘modern-day vaccines have their root in Nazi medical experiments’. The most passionate anti-vaccine view would argue that toxic poisons injected into the body of humans to save lives is pure brainwashing by the medical community, qualifying as ‘the greatest health lie from Medicine’.

On the other hand, using Evidence Based Medicine as a guide would permit the conclusion that any risk or harm caused by vaccines is much less than the risk of harm from the disease itself. Many diseases we vaccinate against such as diphtheria, hepatitis B, measles, meningococcus, tetanus, whooping cough and the flu can kill or cripple children and adults and did so frequently before we had the vaccines. In the past, whereas most vaccines were aimed at children, future vaccines will target adults. We can look forward to seeing combinations of vaccines with five or more components. Eventually we will not even have to fear needles as the vaccines will be administered by skin patches and aerosols. We will be protected against the modern threat of bioterrorism which may try to use anthrax, plague and smallpox against us. In the near future we can even look forward to vaccines against HIV, malaria, tuberculosis and even hypertension.

With these developments, the global vaccine market is expected to grow from US$24billion in 2009 to US$56billion by 2016. The innovations, research and development will be conducted by the giant multinational companies, contract research organizations and in the early stages of preclinical and clinical development by biotechnology companies. Hundreds of millions of dollars will be invested in developing new vaccines with governments supporting the efforts through subsidies, rebates and tax exemptions. The prices of vaccines will continue to be related more to what the market can bear than the cost of production.

Asia is an area of special importance for travelers. Every backpacker will, or should know that they need to be immunized against diphtheria, polio, tuberculosis (BCG), Hepatitis A and B and Japanese B encephalitis. Many will have tried the berry flavored cholera drink and will have taken yellow fever and polio vaccines. For those exploring rural India, rabies vaccination is a worthwhile strategy as is tetanus for anyone contemplating snorkeling or motor cycle riding.

The challenge, therefore, is to develop vaccines and make them available where they are needed most. Diseases such as HIV, malaria and tuberculosis exist principally in poorer countries. Quintiles is a preferred provider to a consortium of 14 global health product development partnerships (PDPs) funded in part by the Bill and Melinda Gates Foundation.

If one can accept the evidence that overwhelmingly supports the benefit of vaccines, then the crux of the most important challenge we face is surely to reconcile the irony that pharmaceutical companies have little incentive to develop vaccines for these diseases due to:
- The minimal financial returns.
- The high risks.
- The inestimable stakes for global consciousness and harmony.

About the Author

Dr. Rebuck heads up the Strategic Drug Development unit of Quintiles in Asia where his team guides clinical and regulatory strategies for clients wanting to develop their medicines in Asia. Previously, he held senior leadership positions in GSK and Pfizer. He was formerly Professor of Medicine at the University of Toronto and a respiratory medicine specialist at the Toronto Lung Clinic.
Despite advances in the understanding of cancer biology, improvements in surgical techniques and radiotherapy, new therapeutic agents and targeted therapies, long term survival remains an issue and better, less toxic treatments are needed. Cancer vaccines with the potential for ease of administration and low side effects are a theoretically appealing form of treatment when compared with that of standard cytotoxic chemotherapy. However, several obstacles need to be overcome before vaccines can be utilized for cancer treatment. Whilst this article will focus on lung cancer, the key points can essentially be applied to all other forms of cancer.

For a cancer to progress to a clinically detectable level, it has to evade the immune system and overcome the host’s “immunosurveillance”. Vaccination must, therefore, be able to induce an effective cellular or humoral immune response capable of tumour destruction, an immune response that has not occurred naturally, despite the presence of foreign tumour antigens. Therefore, the use of adjuvants to augment the anti-cancer immune response becomes of key importance. A second problem is that of choosing a target for vaccination. Ideally, vaccine antigens that are targeted are unique to cancer cells thereby avoiding the risk of the vaccine causing autoimmunity. Over the last 5 years considerable advances have occurred in the understanding of cancer biology, with it now being evident that many different genetic abnormalities and many different “driver mutations”, may be present in similar forms of cancer. This is particularly so in lung cancer, which is the most common cause of cancer mortality and one of the most difficult to treat cancers with the poorest outcomes.

Most of the cancer vaccines in development and in clinical trials are considered therapeutic vaccines, as they are designed for administration to patients already diagnosed with cancer. To date, there are two marketed therapeutic cancer vaccines, the Provenge vaccine approved by the FDA, for prostate cancer and the other a lung cancer vaccine approved by the Cuban
regulatory authority (see below). However, about 900 cancer vaccines are currently in various stages of clinical trials. Whilst the results of many previous cancer vaccines trials have been disappointing, several recent approaches have shown promise and are discussed below.

Cancer Vaccines Already in Clinical Use

Provenge Prostate Cancer Vaccine

Currently the only cancer vaccine approved for use in the USA is Provenge, (Sipuleucel-T), used to treat asymptomatic or minimally-symptomatic metastatic, hormone-resistant, prostate cancer. Provenge treatment requires extraction of the patient’s own blood cells (antigen presenting cells) by leukapheresis, incubation of these cells with the antigen prostatic acid phosphatase (PAP) (present in 95% of prostate cancer cells) and granulocyte-macrophage colony stimulating factor, and re-infusion of the PAP-labelled blood cells into the patient. Clinical trials suggested that Provenge is able to improve life expectancy in advanced disease, by an average of 4 to 7 months. The side effects of Provenge were mostly limited to chills, fever, fatigue, nausea and headache which usually occurred within the first few days of treatment. Although this strategy demonstrates the effectiveness of cancer vaccines, it would be difficult to apply to lung cancer given that, unlike prostate cancer, lung cancer lacks a universal antigen such as PAP. Overall, Provenge has not been a major commercial success, with factors including the complexity of its preparation and its extremely high cost to the patient.

Cuban EGFR-targeted Lung Cancer Vaccine

The Epidermal Growth Factor Receptor (EGFR) is over-expressed in many forms of lung cancer. Moreover, mutations of the EGFR which may lead to excessive activation are found in 15% of Non-Small Cell Lung Cancer (NSCLC) in Caucasian populations. Researchers based at the Centre of Molecular Immunology in Havana, Cuba, have developed a vaccine targeting the EGFR, called CimaVax-EGF. In randomized studies of patients with locally advanced and metastatic NSCLC, treated with initial cytotoxic chemotherapy, this vaccine has been associated with improved survival and was well tolerated with only modest side effects (fever, malaise and myalgia at the time of injection). Currently this vaccine is accepted as standard of care in Cuba although further studies to better define the extent of response and optimal regime of chemotherapy are currently underway in Cuba and other centres.

Lung Cancer Vaccine Trials

The MUC1 gene is part of a group of genes that are responsible for the coding of mucin glycoproteins that are strongly expressed in a large number of different tumour types. MUC1 is suspected to enhance tumour progression and contribute to immunosuppression and in patients with lung cancer; expression of MUC1 is associated with poor prognosis. L-BLP25 (Stimuvax) is a liposome-based cancer vaccine that targets the exposed core peptide of MUC1. It consists of a 25-amino acid sequence specific to MUC1, monophosphoryl lipid A (a non-specific immune stimulant), and a liposomal delivery system. This vaccine is intended to target MUC1 and induce a cellular immune
response against neoplastic tissue that expresses the MUC1 antigen. A Phase IIB trial was conducted in patients with late stage lung cancer who had responded or who were stable after first-line chemotherapy or chemo-radiotherapy. The median survival time was 17.4 months for patients in the L-BLP25 arm, compared to 13 months for patients in the best supportive care arm. The overall safety and efficacy of this vaccine and its effect on survival will be tested in an upcoming Phase III trial.

TG4010 is a suspension of recombinant Modified Vaccinia virus, containing coding sequences for human MUC1 antigen and human Interleukin-2 (IL-2), and is meant to induce both innate and adaptive immune responses. A Phase IIB trial assessed the effectiveness of this vaccine in combination with cisplatin/gemcitabine chemotherapy in patients with locally advanced or metastatic NSCLC expressing MUC1 by immunohistochemistry, and with good performance status. There was an increased response rate and improved progression free survival in the combined treatment group compared with that of the group treated with chemotherapy alone, suggesting that TG4010 enhances the effect of chemotherapy in advanced NSCLC. However, patients in the vaccine treated group did have an increased incidence of fever, abdominal pain and injection-site pain. Post-hoc analysis suggested that a subgroup of patients with normal levels of activated Natural Killer (NK) cells at baseline analysis achieved a more marked response. Confirmatory Phase IIB / III trials are currently underway.

Belagenpumatucel-L is a non-viral, gene-based, allogeneic tumour cell vaccine. It consists of 4 lung cancer cell lines. An open label, three-arm, randomized phase II study of low medium and high dose showed that patients who received high doses showed a greater survival advantage than the patients who received low dose. The efficacy and safety of this vaccine is being further investigated in the ongoing Phase III trial where the primary endpoint is survival.

Advax™ is a novel polysaccharide vaccine adjuvant that is being developed by Vaxine Pty Ltd in Adelaide, Australia across a range of vaccine indications including cancer. Promising enhancement of cancer vaccine efficacy has been obtained with Advax™ adjuvant in pre-clinical studies and it is hoped that human cancer vaccine trials including the adjuvant will commence shortly.

**Immunoglobulin E Anti-cancer Therapy**

Recent interest has focused on the potential role of Immunoglobulin E (IgE) as a mediator of anti-cancer effects. As IgE comprises only 0.02% of the total antibody in humans, specific anti-tumour IgE faces less competition for cell surface receptors than other immunoglobulin subtypes. Moreover, IgE is able to induce antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis via high- and low-affinity receptors, FcεRI and CD23. As the affinity of IgE for FcεRI is two to five orders of magnitude higher than that of IgG, IgE should potentially be more potent in tumour destruction. Thus far it has been difficult to specifically generate IgE antibodies in response to vaccination, which more typically induces IgG antibodies. Recently an animal model has been developed in which IgE was induced by epitope-specific vaccination against the tumour antigen HER-2, using an oral immunization regimen, fed under concomitant gastric acid suppression. However, considerable further research would be required before this model could be translated to human trials.

**Conclusions**

New therapeutic strategies are required in the treatment of cancer. Vaccines and other immunotherapies offer an attractive alternative to current treatments such as chemotherapy. After failures of many cancer vaccine trials and widespread loss of faith in the field, signs of hope are emerging with recent commercialization of Provenge, the first FDA-approved human cancer vaccine. This has helped to re-invigorate the cancer vaccine field, with renewed research into identification of additional tumour antigens to be used as vaccine targets, investigation of new vaccine adjuvants to better enhance the immunogenicity and potency of cancer vaccines, and exploration of new vaccine delivery techniques such as DNA vaccines, which may be able to better stimulate an anti-tumour cytotoxic T-cell response. Hence, while it has been a long road travelled, cancer vaccines are currently undergoing a major revival, and it is hoped that this will result in additional regulatory approvals in coming years. Whilst Provenge has not been a major commercial success, this largely reflects the fact it is a complex dendritic cell (DC) vaccine. Without a doubt, a more traditional protein-based vaccine that doesn’t require the use of the patient’s own white blood cells is likely to be much more attractive to patients and doctors and thereby more commercially successful.

**References**


About the Authors

**Nikolai Petrovsky** is Research Director of Vaxine, an Australian biotechnology company, Director of Endocrinology and Professor of Medicine at Flinders Medical Centre/Flinders University, and Secretary-General of the International Immunomics Society. He is funded by the US National Institutes of Health for biodefense vaccine development. He has taken four vaccines to the clinic and has authored over 100 scientific papers and book chapters.

**Dimitar Sajkov** is a founding Director of the Australian Respiratory and Sleep Medicine Institute and runs the respiratory clinical trials unit at Flinders Medical Centre in Adelaide, South Australia. He is a senior Consultant Physician, actively involved in translational research programs in adjuvanted vaccines, pulmonary hypertension, COPD and sleep apnea. He is a recipient of the Australian Thoracic Society prize for physiological research and best presentation in sleep and physiology in 2002, when he was appointed as a Senior Consultant at the Flinders University Medical Centre and a senior lecturer at the Flinders University. His major area of research is related to COPD, pulmonary hypertension, influenza vaccines and sleep apnoea. He is also a Director of the Southern Sleep service in Adelaide. He is a recipient of numerous research grants, including NHMRC, and an author of over 25 peer reviewed papers, 70 published abstracts and invited peer reviewer for many major professional journals. He is a current ACCP Regent for Australia and has been invited as a guest speaker at International Conferences.

**Rohit Philip** graduated with a Master's degree in Medical Biotechnology from Flinders University, Adelaide, South Australia, in 2006. He has worked in various research centres in Adelaide, including the South Australian Research and Development Institute (SARDI) and the Bone and Joint Research Laboratory at the Institute for Medical and Veterinary Science (IMVS). Rohit currently works at the Southern Sleep laboratory at Flinders Private Hospital and Flinders Medical Centre. He recently joined the Australian Respiratory and Sleep Medicine Institute in 2012 as a PhD candidate in lung cancer vaccines.

**Jeffrey Bowden** is an Australian Thoracic Physician with a long standing interest in the treatment of lung cancer, and currently Head of Respiratory, Allergy and Sleep Services in the Southern Adelaide Local Health Network. He is a member of the Australian Lung Cancer Clinical Trials Group, and Co-convener of the recent Australian Lung Cancer Conference in held Adelaide.
Virus-based vaccines are arguably society’s most successful modality for the prevention of deadly human and veterinary diseases. However, somewhat ironically, vaccine manufacturing has long resisted progress. For many vaccines, manufacturing processes are still dominated by outdated, slow, and unreliable chicken-egg based or primary cell culture methods [1].

To improve reliability and deal more effectively with the threat of rapidly emerging viral pandemics, the vaccine industry and organizations such as the World Health Organization (WHO) are increasingly advocating the use of continuous cell lines for vaccine production [2-5]. However, due to stringent regulatory guidelines for both human and veterinary vaccines, available continuous cell lines for vaccine manufacturing are still limited. Prominent
examples include Vero African green monkey kidney cells, Madin-Darby canine kidney (MDCK) cells, and BHK-21 cells. In addition to these continuous cell lines, a handful of human diploid cells such as MRC-5, FRhl-2, and WI-38 have been used to make human vaccines [6].

These cell lines provide well defined, reliable, and in the case of continuous cell lines, easily scalable substrates to grow vaccines. However, in many cases low virus yields are obtained using these substrates. Consequently, manufacturers are constantly looking to improve vaccine production yields from cells, often empirically through process optimization. For companies looking to adopt new and more efficient technologies to this end, the decision comes down to simple economics: does the potential increase in vaccine yield justify the overall cost associated to deviating from the methods already in place? With existing technologies, the answer to this question is unfortunately often the negative, preventing the adoption of modern continuous cell-based methods for many vaccines. This is most notably the case for influenza vaccines, which are still predominantly made using chicken eggs. It is clear that there is a pressing need and an emerging market for innovations that will substantially and economically improve vaccine yields from cultured cells [3, 6, 7].

Likely because of the direct correlation between cell substrate quantity and viral vaccine output, most attempts at improving vaccine yields from cell cultures have focused on improving cell growth properties. Such strategies include optimizing chemically defined media, novel bioreactor technologies, and the selection or design of continuous cell lines with improved growth characteristics. For example, genetically engineered PER.C6 cells (J&J/Crucell) have been reported to grow at very high densities in suspension without the need for animal serum [8]. As a result of these and other characteristics, PER.C6 cells are of high interest to many biotherapeutic companies. Regardless of the success of PER.C6 cells, the use of designer cells for vaccine manufacturing is only in its infancy and to our knowledge there are still no approved vaccine products made with these or other designer cell lines.

**Cellular antiviral defenses: overcoming the first hurdle**

The cellular antiviral defense is triggered upon viral-infection of a cell and is a common and primary hurdle for all replicating viruses [9, 10]. As invading parasites, most naturally occurring virus strains express virulence proteins that block the cellular antiviral response and thus facilitate virus propagation [11-15]. Virulence proteins in disease-causing viruses are evolutionarily adapted to hijack the antiviral defenses of the specific species, tissues, and cells in which they cause disease (eg. Human airway epithelial cells for human influenza virus). The ability of virulence proteins to overcome antiviral defenses can be compromised in cells that are not the virus’ natural target. Similarly, mutations within these virulence proteins can lead to viral attenuation and/or restricted host cell range [13, 16-18].

While reducing virulence is generally desirable to make safe vaccines and other virus-based therapeutics, this also creates viruses that can grow poorly when forced upon non-host manufacturing cell substrates. To get around this problem, some groups have adapted vaccine strains to improve their growth characteristics in selected manufacturing cells through directed evolution [16, 19, 20]. While this approach can be effective, it necessarily leads to genetic changes in the vaccine, desirable or not, due to its adaptation to the new host cells. Such genetic adaptations on behalf of the virus can be expected to provide a growth advantage by optimizing the virus’ ability to co-opt cellular resources in a new context while also effectively retaliating against the new host cell’s antiviral defenses. However, this may also impact the vaccine’s activity and/or safety.

Another potential approach to improve the growth of vaccines from cell lines is to effectively disable the cellular antiviral defenses of manufacturing cells to fully permit growth of even severely attenuated vaccines. While gene silencing and genetic engineering approaches can and have been considered to this end [21], they are likely to be too costly and/or insufficiently comprehensive in light of the complexity and redundancy of antiviral defenses. In addition, the genetic engineering strategy is inherently time/resource consuming given the heavy regulatory burdens placed upon new cell line derivatives for vaccine production.
Viral sensitizer technology: a welcome boost from cancer

Surprisingly, one novel approach that can be used to circumvent genetic manipulation of viruses and continuous cell lines comes to us from the field of cancer therapeutics. In the last decade or so, the use of attenuated and tumor-specific oncolytic viruses for the treatment of cancer has become a real possibility. Indeed, Asia can certainly pride itself as being the first to adopt this technology as evidenced by China’s approval of Shanghai-based Sunway Biotech’s H101 oncolytic adenovirus for the treatment of head and neck cancer, well in advance of the looming approval of similar agents in North America and Europe [22].

One well recognized issue in the field of oncolytic virotherapy is that tumors often resist infection by these therapeutic agents due to the cellular antiviral response [23]. To overcome this problem, we have recently discovered a group of compounds that robustly enhance virus growth in cells. As a whole, what we have termed viral sensitizer technology (VST) encompasses a collection of compounds that work by broadly and effectively disrupting cellular antiviral defenses.

While we initially discovered this technology in the context of oncolytic virus therapy using a vesicular stomatitis virus [24], where over 1000-fold increases in viral titers were obtained in some cases, we have since found that our VST can be used to increase the production of vaccine strains in manufacturing cell lines. For example, using VST in continuous BHK-21 cells we have been able to observe increased yields of modified vaccinia ankara by 10-fold, reaching approximately 45–times higher yields than what can be produced in parallel using industry-standard primary/ non-continuous chicken embryo cells. Likely owing to the universality of antiviral defenses as a hurdle for efficient viral growth, we have found that such increases in viral yields can be observed for several DNA and RNA viruses and in many different types of continuous cell lines as well as in human diploid cells. It is easy to imagine that such improvements in vaccine yields could have a drastic impact on both the cost and the manufacturing time per vaccine unit.

So how safe is this approach? While we can expect that VST will be held to the same regulatory scrutiny as designer cells and other related technologies, our lead VST compounds for vaccine applications have so far not shown signs of mutagenicity and are below the limit of detection in crudely purified viral preparations. To date, we have also not observed any direct impact of VST on the viruses produced when investigating basic viral characteristics (virus protein expression/size, ability to replicate etc.).

Altogether with VST’s very low cost in relation to other approaches and associated high vaccine yield, VST is an ideal solution to improve existing virus-based vaccine manufacturing processes and for implementation in future vaccine production methods. Because of the obligatory regulatory approval process for all new vaccines/processes, VST is expected to be most beneficial for new vaccine candidates, particularly those that do not grow to sufficiently high titers using available substrates. As alluded to earlier, this is often the case for live attenuated vaccines. It is also foreseeable that VST can be used in addition to technologies that aim to improve the growth characteristic of cells such as chemically-defined media, advanced bioreactor technologies, and designer cell lines. We believe that the Asia-Pacific biotechnology community is a rich source for strategic partnerships to evaluate VST given that market growth for the vaccine sector in the region is expected to grow tremendously in the next few years.

References

Jean-Simon Diallo obtained his Bachelor’s degree in Biochemistry at the University of Ottawa and a Master’s in biochemistry at McGill University. He earned his Ph. D in Molecular Biology at the Université de Montréal and subsequently went on to do a postdoctoral fellowship at the Ottawa Hospital Research Institute (OHRI) where he worked on improving oncolytic virotherapy using small molecules. An Assistant Scientist at the OHRI, his research focuses on manipulating the cellular antiviral response using small molecules for a wide range of virus-based therapeutics applications.

About the Author
Influenza has been a major infectious disease that affects public health worldwide. Three pandemics of influenza occurred in the 20th century, causing tremendous loss in human lives and the economy worldwide. The first pandemic of the 21st century occurred in 2009–2010. Immunization has been the most effective and inexpensive measure in controlling the spread and seriousness of the disease.

Influenza vaccines are produced from the specific influenza viruses and the viruses have been prepared in embryonated chicken eggs for over 70 years. This egg-based production process has inherited many drawbacks. For example, the eggs may be susceptible to the virus, or the virus may not be able to grow efficiently in the eggs. The eggs should come from healthy hens and should be ordered 6 months in advance, dead and defective eggs should be detected and discarded during the production process, and the used eggs should be treated and disposed at high cost. The hemagglutinin of the viruses grown in eggs may exhibit antigenic alterations and limit vaccine effectiveness. Virus harvests collected from eggs are always more or less contaminated with microorganisms that may affect the subsequent purification process and the quality of the vaccine products. And, the residual egg components in the vaccine products may cause allergic reactions in some sensitive people. Nonetheless, large quantities of influenza vaccines cannot be timely produced by egg-based method to meet urgent needs, as witnessed during the 2009 H1N1 pandemic. This problem has led to the incentive actions taken by several authorities to promote development of new production methods, including cell culture.

In addition to overcoming the drawbacks associated with egg culture as cited above, production of influenza vaccine in cell culture may also offer many distinct advantages over egg culture. For example, it allows rapid initiation and scale-up of production in the event of urgent needs. It provides well-controlled, contamination-free cell cultures for use by the virus to grow, virus preparation of high purity for easier subsequent purification process, and high degree of product batch-to-batch consistency. Therefore, quality of the vaccine products will be better and more consistent from batch to batch. In fact, the vaccine products will contain much less endotoxin, a fever-causing substance derived from certain contaminated bacteria.

Cell cultures have been used in the production of polio and hepatitis A vaccines,
Figure 1. A complete set of BelloCell-500 system consisting of a BelloStage, 4 pieces of BelloCell on the stage and a control panel. The bellows and the medium are pushed up and down to affect aeration and mixing.

Figure 2. A schematic drawing of the Tide Bioreactor system. Single-use bags can be used for Vessels A and B.
among others. Active development of cell-based influenza vaccine production processes began in early 2000's. Many cell lines, including Madin-Darby canine kidney (MDCK), PER.C6®, and Vero cells, have been used. Vaccines produced in cell MDCK and Vero with serum-free media have been shown to be safe and efficacious 3,4, and two cell-based products were approved in Europe in early 2000's 5,6.

Currently, a variety of cell culture systems are used in vaccine production, including T-flasks, cell cubes, cell factories, hollow fibers, roller bottles, stir-tank bioreactors and shaking bags. All these systems have some drawbacks themselves. For example, roller bottles and cell factories are capacity- and space-limited, labor intensive, and prone to microbial contamination. Stir-tank bioreactors used in large-scale production require expensive and space-taking pipings for utility supply and clean-in-place (CIP) and sterilization-in-place (SIP) systems. In addition, the intensive agitation required to enhance mass transfer in stir tanks causes damage to the cells being cultured, leading to release of cellular material and impairment of the purity of the virus harvests.

Shaking bag system such as the WAVE system is an improved one that can have a culture capacity up to 500 liters. It is a single-use disposable system, in which a new, pre-sterilized bag is used each time, and does not need either the CIP or SIP system. However, like the stir-tank systems, the system is operated under extensive, foam-generating shaking and requires addition of a toxic anti-foam agent for proper aeration.

Recently, a completely new bioreactor system called Tide Bioreactor system for anchor-dependent cells was introduced by Cesco Bioengineering Co., Taiwan. This system applies a special agitation mechanism that maximizes mixing and aeration without causing damages to the cells being cultured. In other words, culture medium is moved in and out of the culture vessel just like the tide moving up and down the beach, allowing the wet cells to intermittently and directly be exposed to the air. The degree of aeration and mixing is automatically controlled by mode of medium flow.

Essentially, the Tide Bioreactor system is composed of a culture vessel (A), a service vessel (B), and a reciprocal flow pump between the two vessels. Both vessels can be disposable. Vessel A contains both culture medium and microcarrier chips. Vessel B, which can be 10-fold or more bigger than Vessel A, contains a mixing device and serves to receive the medium from vessel A. Vessels A and B can be single-use, disposal bags. During operation, the culture medium is moved by the pump between the vessels, and mode of the movement, e.g., flow rate and holding time, is adjusted to optimize conditions for cell attachment, cell cultivation, and viral propagation. Vessel A has different capacities, and can hold culture media from as little as 500 mL (BelloCell-500, Figure 1), 2 liters (TideCell-2, Figure 2) to as much as 100 liters (TideCell-100). Based on cell mass productivity, one BelloCell is equivalent to 10 roller bottles (RB-850). Cell density in Vessel A is normally 10 times higher than those cultured by conventional method. Therefore, at the time of viral propagation, volume of the medium can be 10-fold or more than that for cell culture. Furthermore, mode of medium flow can be programmed and controlled automatically. And, the whole process can be linearly up-scaled.

Medigen Biotechnology Corporation has been evaluating the Tide Bioreactor system for its suitability for the production of influenza vaccines since early 2000. BelloCell-500 and TideCell-10 bioreactors, BioNOC-II microcarrier chips, and PlusMDCK serum-free medium were purchased from

<table>
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<th>Specification*</th>
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<th>Residual DNA (ng/mL)</th>
<th>Endotoxin (EU/mL)</th>
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*Current specification for egg-based vaccine except for residual DNA
**Assumed value

Table 1. Quality of bulks of influenza 2009 H1N1 and H5N1 vaccines produced in Tide Bioreactor system
Cesco Bioengineering. Vessel A was a modified 10-L serum bottle, and Vessel B was a single-use 50-L bag sitting on a shaker. Pre-qualified MDCK cell line and influenza seed viruses (H1N1, NIBRG-121; H5N1, NIBRG-14) were purchased from the National Health Research Institute (NHRI), Taiwan. Four batches of the H1N1 vaccine and 3 batches of the H5N1 vaccine were produced at NHRI’s cGMP facility. Process parameters, including cell/virus inoculum sizes, trypsinization conditions, medium changes and virus propagation conditions, had been determined in advance. Vessel A in the Tide-10 bioreactor can hold up to 10 liters of culture medium. But, only 50% of the capacity (i.e., 275 g of BioNOC II and 5 liters of medium) for a 50-liter virus harvest was used in the present study. Basically, the upstream process included expansion of the cell culture and propagation of the virus. The expansion stage began with inoculation of one vial of 1 x 10⁶ viable frozen cells onto two 75T-Flasks and incubated at 37°C for 3 days. The culture was then expanded by sub-culturing through RB-850 and the BelloCell-500, and finally in the TideCell-10. Culture conditions, such as pH, temperature, dissolved oxygen, glucose consumption rate, cell density, lactate concentration were monitored and/or controlled during the process. The whole culture process took a total of 26 days. The cell density in Vessel A was around 2 x 10¹⁰/mL at the time when viral infection and propagation began. The hemagglutination (HA) titer, a measurement for virus concentration, at harvest was 1,024 as determined by the standard method. A total of 7 batches of virus harvest were purified by conventional clarification-centrifugation-diafiltration process, and detoxified with formaldehyde to make vaccine bulbs. And from these, two batches (one H1N1 and one H5N1) were further processed with aluminum hydroxide gel to make vaccine products. Both products met all release criteria (Table 1), passed pre-clinical toxicity and immunogenicity tests, and were stable at 4°C for at least one year. A Phase I clinical study for the H5N1 vaccine product, Lot AT-301, will begin in the third quarter of 2012. Table 1 also indicates that the control vaccine, which was produced by using Roller Bottles, contained much more residual cellular proteins.

In conclusion, we have been able to satisfactorily produce pandemic H1N1and H5N1 vaccines for clinical study by using the Tide Bioreactor system. This system has all the benefits associated with other single-use bioreactors. In addition, the Tide Bioreactor system offers the best mass transfer method without causing damages to the cell being cultured.

The study was conducted by team members including Queena Lin, Rayd Ho, Jianming Chen, Allen Wang and Tingwan Lin.

References

About the Author
Wenlii Lin has accumulated his hand-on experience in vaccine basic research, product and process development, cGMP production and management during the past 30 years. His career in the field began with the discovery of two compounds from the culture fluids of Streptomyces spp that inhibited the enzymatic reaction of the influenza A neuraminidase and the infection of the viruses in mice while at The University of Tokyo Graduate School. Since then, he has worked on a variety of vaccines at several institutions. Being a Visiting Associate at the Center for Biologics Evaluation and Review (CBER, then BOB), FDA, he studied the biosynthesis of the Escherichia coli capsular polysaccharide antigen. He was a Group Leader – Product and Process Improvement at Lederle Laboratories, VP-Manufacturing at North American Vaccine Corp., CEO/President at Adimmune Biotech Corp. and CEO at Medigen Biotechnology Corp. Dr. Lin’s current focus is on the development and commercialization of pandemic influenza vaccines and EV71 vaccine using the TideCell Bioreactor system.
A PBN speaks to the CEO of Morflora, Dr. Dotan Peleg on his revolutionary technology that hopes to contribute improvements to the agricultural industry. His TraitUP Plasmid technology has even garnered the attention of the U.S Department of Agriculture with its potential applications that aspires to benefit farmers from both developed and developing countries.
APBN: Your TraitUP Plasmid technology involves exposing the crop seeds to solutions containing the plasmid DNA and genes of interest. How similar is this to RNAi, where an organism is exposed to RNA strands that induce suppression of certain genes of interest, without changing the DNA of the organism itself?

Dotan Peleg: You are right RNAi acts by suppressing the genes whereas the TraitUP plasmid acts by expressing genes of interest. The plasmid is a circular double strand of DNA that replicates within a cell independent of the chromosomal DNA. This is Morflora’s first company secret. What makes it even more exciting, is we managed to induce the majority of the plant’s cells to express the genes, whereas previously only specific cells could do this.

APBN: Once the TraitUP Plasmid is used on one batch of plants, will they stably pass on the plasmid genes to successive generations via sexual / asexual propagation?

Dotan Peleg: This is a concern often raised by anti-GMO and pro-organic groups. Our experiments have shown no presence of the plasmid in the F1 generation. We also disproved spreading of the plasmid from one plant to another. There is also no plasmid transfer from plants to animals. The virus that forms the basis of this technology does not infect animals or human beings.

APBN: Is it possible to induce expression of traits of interest by exposing a plant to the plasmid at stages of development after seed – such as seedling, adult, etc?

Dotan Peleg: Yes, this is also possible. However, we are currently focusing on the seed stage because once you treat the seeds, most of the pesticides and fungicides you normally would have to use at later stages are rendered unnecessary. This drives down the cost of farming dramatically, and is the key thrust of our technology.

APBN: Can you give us an idea of possible lengths of your genes of interest in terms of base-pairs?

Dotan Peleg: We have developed our technology to the extent that DNA lengths of up to 10,000 base-pairs can be incorporated into the plasmid. This is almost 10 times the average size of genes incorporated into other vectors. We are able to deliver not just single genes, but multiple genes and even operons.

APBN: If the system can express traits to prevent/resist disease, can it be used for other traits like improved nutritional quality? Can you comment on any other genes you intend to express in this regard?

Dotan Peleg: Absolutely. These are all traits with good commercial interest and Morflora may explore partnering other companies to research how to deliver these traits using our technology in the future. As for examples, I can only say we are very interested in developing some genetic material that may dramatically accelerate growth regulation, and even traits that give resistance to abiotic stress such as drought tolerance.

APBN: What exactly has got the U.S Department of Agriculture so excited about your technology?

Dotan Peleg: There’s a section within the US Department of Agriculture that specifically targeted to identify crop-protection technologies for specialty crops and once they discovered that technology, they help that technology to grow and enter the market by funding the laboratory process of the technology and representing the company in front of the BPA – the Bio Protection Authority. This is the kind of partial funding we are receiving from the US Department of Agriculture. According to their study, the investment in introducing new plant-protection technology for specialty crop will be almost a 100 times fold in investment in preventing the damages present in the agriculture segment in the United States.
APBN: Referring to the article, "Homegrown Israeli idea for conquering the world food shortage" on the Haaretz website, it says the company founders are unable to fully explain how their technology works. Can you elaborate more on this?

Dotan Peleg: Well we do understand the replication process that happens in the cell, specifically in the nucleus. It replicates from a double stranded DNA but this is very much unlike the way viruses replicate because viruses specifically the TYG which is the ancestor of our technology, it uses a single strand DNA which suggests a totally different replication mechanism. We know one of the proteins involved and have some ideas on how to investigate that. We would certainly want to carry on with that research because the results can shed new light on functional genomics in plants. From a broader perspective, we know have a tool that scientists can use to deliver trait or genetic material to the start for exploring that trait in the target plant. Functional genomic researchers in plants, their work is based on years of trial and error experiments often in modern plants very much different from the target plant of research. We can now bypass breeding, genetic engineering and speed up research so scientist can explore the characteristics of inserted genetic material into the target crop.

APBN: Lastly, if and when the technology gets commercialized, which country/countries’ agricultural systems do you think would most benefit from it? Any reasons?

Dotan Peleg: First of all, our mission is to serve the planet – we want to remain an independent player. We want to serve all the countries, the feed companies and the agriculture segment. I believe there are many countries that can benefit from it. Especially in countries in which there is a need to reduce dependency on chemicals, the infrastructure of agriculture makes the crops be more susceptible to viruses, diseases and bacteria and to countries which are susceptible to pandemic spread of bacteria and viruses through insects and they cannot stop the epidemic via insect vectors and they need to acquire an immunization to protect their plantation and crop. Countries in which –as you suggested before- the nutrition value of the crops must be enhanced and the total yield needs to be enhanced. I believe that we can contribute to a large segment of the globe which is our goal; vision and aspiration which we hope prove to be successful because we are looking at a very concerned future for agriculture. The demand is becoming a steep and sharp incline whereas the farming per capita is on a sharp decline and even today with modern agriculture, we can still witness an average 25% of global crop is virus infested in agriculture. If we only make a modest contribution to eliminate some of these unprecedented damages, we would be very pleased with that.

About the Author

Dotan Peleg joined Morflora after founding and managing several high-tech start-ups. Formerly CEO of HyNEX, he led the company to a $127M acquisition by Cisco. Dotan brings extensive expertise in setting up ventures, developing new products, and breaking into markets with new technologies. He is suma cum laude graduate in Physics from the Tel Aviv University.
You might already be in the Biotech business or have a technology you would like to commercialize. Or you might be in a large company looking to in-license or acquire technologies to add on to an existing portfolio. You are familiar with the usual factors influencing your business, revolving around capital investment, manpower, market demand and customer service, but are you aware of an emerging area that might also affect you – intellectual property rights (IPR) and protection?

Global Trends

A recent report, commissioned by the Biotechnology Industry Organization (BIO), a non-profit US-based trade association, serving biotech companies world-wide, illustrated how biotechs, both in mature and emerging economies, can benefit from proper understanding and usage of intellectual property rights (IPRs). Pugatch et al (2012) reviews a growing trend of IPR activities through a variety of indicators, such as patenting activity, technology transfer, licensing activities, partnerships and collaboration, all suggesting the value and importance of IP in the biotech sector.

The report highlighted a general uptrend in patenting activity over the last few decades, as countries across the world move from engaging in classical manufacturing and production industries to knowledge-based activities. More impressively, statistics from the Organization for Economic Co-operation and Development (OECD) show that global biotech patents have grown from a mere 12 patents in 1977 to 9,339 patents in 2009. This sharp increase in biotech patent applications points to the notion that individuals and organizations worldwide have begun to see the value of IPR in biotech innovation, and patenting activities reflect a desire to protect and disseminate it. Whilst most of the patents are still filed in mature economies like the United States and the 27 European Union countries (constituting 69% of the total number of patents in 2009), there has been a shift in patenting activities to emerging economies like Asia, Russia and Latin America. Asian countries like China, India, Japan, Korea, Singapore and Taiwan are among the forerunners in the last decade, accompanied by other emerging countries like Argentina, Brazil, Israel and Russia (see Figures 1 and 2).

Pugatch et al added that countries with active patenting activities tend to have effective technology transfer frameworks. Organizations engaging in biotech R&D activities in these countries, in particular the publicly-funded ones derive many collateral benefits from these technology transfer activities. Apart from being able to commercialize their basic research, they generate revenue from licensing fees and royalty payouts from commercial organizations that partner with them or license their technologies. Additionally,
Figure 1: Number of biotechnology patents filed in China, Korea, Israel and Japan under PCT from 1977 to 2009 taken from OECD (Source: Pugatch et al 2012)

Figure 2: Number of biotechnology patents filed in Brazil, India, Russia, Singapore, Taiwan and Argentina under PCT from 1977 to 2009 taken from OECD (Source: Pugatch et al 2012)
these countries see growth and development of industries around these technological developments.

Indeed, excellent technological innovation should be accompanied by good technology transfer and translational activities, otherwise, a scientific discovery will remain, well, a discovery. Something is only considered an invention when it is accorded utility and people can benefit from the use of it. Of course, this makes it rather challenging for biotechnology in today’s world, especially with the advent of genetic engineering and genomics, for which there is an increasing trend in the discovery of genes and other natural biological entities which regulate and control key biological processes, which may in turn influence the application of drugs and therapies. One then begins to question if it makes sense to patent, protect and thereby restrict the dissemination and use of these entities. Surely, mankind must be allowed to use this information freely to benefit from these “discoveries”?

Pugatch’s report further discusses the influence of IPRs in upstream innovation and commercialization of biotechnology, citing global debates on whether these issues actually promote or hamper biotech development and application. Some protagonists advocate IPR activities as important in motivating continual upstream research and investment in R&D, while others claim that long-drawn and complicated IPR processes may discourage biotech development and even affect the access of some developing nations to critical pharmaceuticals. Hettinger (1995) was quoted saying that “the patenting of biotechnology – in particular genes and organisms – has not contributed to biotechnological innovation and should be discouraged”. However, more recent studies by Walsh et al (2003, 2005) show no direct evidence that patenting activities or processes hinder or delay research projects or innovation. On the topic of influence on access to medicines in developing countries, whilst the average prices of drugs under patent regime are higher than non-patented ones; multi-national drug companies have made an effort to tier the prices of these drugs according to per capita income across countries. In other words, the prices of patented drugs in lower-income countries tend to be lower. A study done by Attaran noted that essential medicines are hardly patented in poorer nations (less than 2%), but yet access to these medicines are limited, suggesting other reasons (for example poverty and distribution networks) besides patenting activities, for the restricted access to critical medicines observed in these countries.

Often, successful biotech or drug development commercialization involves...
partnerships and collaborations between upstream R&D organizations and commercial biotechnology or pharmaceutical companies. A key part of this process is the identification and matching up of suitable research and commercialization partners. As IPR activities strengthen in many countries, companies have to navigate carefully through the IP landscape to identify the right partners to license technologies from or collaborate with. Many companies and R&D organizations benefit from schemes or services that assist them in the sourcing, identification, matching and negotiation processes. An emerging field of IPR activities is the facilitation of transactions by IP intermediaries. In a recent report by Hagiu and Yoffie (2011), several types of IP intermediaries are mentioned – these include patent brokers, non-practicing entities (NPEs), defensive patent aggregators, online marketplaces or portals and live IP auctions. Patent brokers are people who facilitate the sale and purchase or licensing of IP between organizations and usually take a success-based commission from the sales price or upfront fees. As the market for IP transactions is still conservative, many patent brokers offer extended services that may include consultancy, technology sourcing, and negotiation and technology transfer assistance. Patent brokers do not usually acquire or own IP. In contrast, NPEs are organizations that acquire patents in order to capitalize on payouts derived from patent arbitration and litigation processes. On the flip side, defensive patent aggregators represent clients in the acquisition of patents so as to lessen their risks or counter the threats posed onto them by NPEs. There is also an emergence of online portals that facilitate the posting, matching and trading of IP. Again, these facilitation models may involve pure trading of IP or a combination of IP and technology transfer services. Last but not least, there are live auctions facilitating the sale of IP, where a single or bundled IP is sold to the highest bidders, very much like in other regular auctions. Such emerging services show a growing interest in the value of IP and the commercial viability of activities supporting IPR transactions.

**Trends in Singapore**

Did you know that The Global Competitiveness Report of the World Economic Forum 2011-2012 ranked Singapore as the first in Asia and the second in the world for IP protection? In Figure 3, Singapore is seen amongst the forerunners, alongside Japan, Korea and Israel, showing a high Patent Rights Index (PRI). The PRI is a standard measure of the cross-national strength of patent rights protection as well as the IP environment in these countries. It is derived based on criteria such as membership in international patent agreements, extent of coverage, duration of protection, enforcement provisions and restriction on patent rights. This strength in IP protection has a direct impact on the inward flow of foreign direct investment.

![Figure 4](https://example.com/figure4.png)

*Figure 4: Inward Foreign Direct Investment stock, annual, 1980-2010 from UNCTAD. US Dollars at current prices and current exchange rates in millions (Source: Pugatch et al 2012)*
REVIEW

(FDI) to Singapore. Over the years, Singapore has seen a steady increase in inward flow of FDI, and is now one of the leading countries receiving FDI, alongside China and Brazil (Figure 4). On the biopharmaceutical front, a similar index used to measure the strength of pharmaceutical IP protection shows that the stronger the IP protection is in a country, the more it will receive biomedical- and pharmaceutical-related FDI as well as clinical trials. As seen in Figure 5, Singapore is one of the top recipients of biopharmaceutical FDI and clinical trials, next to the US and UK.

The Singapore government recognizes the importance of continual support of innovation, technology development and IP protection, and constantly introduces schemes and programmes to encourage the flow of technology from discovery to commercialization. Recently, the Singapore Ministry of Trade and Industry launched a new initiative under the Research, Innovation and Enterprise (RIE) 2015 Plan, to provide IP intermediation assistance to companies in Singapore seeking to upgrade their businesses through innovation and technology development. Intellectual Property Intermediary (IPI) was incorporated in April 2011 to provide local enterprises with services including technology scanning, assessing, sourcing and matching, to facilitate IP transactions. In addition to consultancy and intermediation activities, IPI also runs an online portal where global technology providers can post their offers so that companies with technology needs can easily search for and locate matching solutions or capabilities.

"Indeed, excellent technological innovation should be accompanied by good technology transfer and translational activities, otherwise, a scientific discovery will remain, well, a discovery. Something is only considered an invention when it is accorded utility and people can benefit from the use of it."

Figure 5: Strength of Pharmaceutical IPRs in relation to Foreign Direct Investment (FDI) in Clinical Research by Pugatch & Chu (2011)
(Source: Pugatch et al 2012)
Pauline Tay currently spearheads the Healthcare and Biotechnology portfolio at IPI’s Intermediary Division, focusing on technology assessment, scanning, sourcing and matching for industries. With a PhD in Stem Cell Biology, and 8 years of experience in R&D at a start-up, overseas universities and A*STAR’s Institute of Medical Biology, Pauline has an extensive network with local and overseas research, technology and licensing communities. Prior to that, she spent 3 years in research administration at A*STAR, and another 3 years as a trainer and consultant at the Singapore Productivity and Standards Board (PSB).

For more information, visit IPI’s website at www.ipi-singapore.org

References


About the Author
The generic pharmaceutical industry is considered one of the fastest growing segments of the global pharmaceutical market. In recent times, it has seen a number of major acquisition deals, such as Watson Pharmaceuticals’ acquisition of Actavis and Sandoz’s acquisition of Fougera Pharmaceuticals. These transactions are indicative of three significant developments among major players within the generic pharmaceutical industry; specifically, generic pharmaceutical companies are increasingly focused on growing in size, moving into specialty areas and expanding regionally.

Growing in Size
In April 2012, Watson Pharmaceuticals announced that it was acquiring Actavis for 5.6B USD, to form the third largest generic pharmaceutical company in the world. With a market share of about 5%, the ‘new’ company will surpass Mylan, which has a market share of less than 4%. Still, it clearly trails behind the market leaders Teva and Sandoz, which have market shares of 11% and 9% respectively. This major deal is currently being reviewed by the US Federal Trade Commission, but is expected to close by the end of the year.
A Little About Actavis

Actavis was founded in 1956 and grew from being a small Icelandic company to become a major player in the global generic industry. With over 10,000 employees, a presence in 40 countries and annual sales of 2.5B USD in 2011, it was among the top 10 generic companies in the world. Its growth was driven by many acquisitions and this became problematic. During the financial crisis, the company was in distress and its main shareholder, Thor Björgólfsson had to cede his shares in the company to creditor Deutsche Bank in 2007. In 2011, the company moved its headquarters to Zug and became a Swiss company.

In early May 2012, Sandoz, which is the generic pharmaceutical division of Novartis, announced that it was acquiring specialty dermatology generics company Fougera Pharmaceuticals for 1.5B USD in an all-cash transaction. Fougera Pharmaceuticals was originally part of Nycomed, which was headquartered in Zurich. In 2011, Takeda acquired Nycomed, but excluded Fougera Pharmaceuticals from the deal.

These deals are motivated by a number of factors. With the acquisition of Actavis, Watson Pharmaceuticals’ overall annual revenue is expected to grow to 5.7B USD. In this instance, it is about size and the advantages that come with being a larger player within the industry. For Watson Pharmaceuticals, one key consideration is the deeper market penetration and regional expansion opportunities that come with the acquisition. It stands to benefit from Actavis’ strong presence in Russia, Bulgaria, Spain, Romania, Turkey and Indonesia. Furthermore, with an enlarged product portfolio, offering a very wide range of different formulations, the company will have greater ability to penetrate the market. In the US for example, Watson Pharmaceuticals’ established distribution channels will facilitate the flow of Actavis products into the US market.

The acquisition will also give Watson Pharmaceuticals greater capacity for production and R&D. The deal presents the company with an opportunity to improve its product pipeline – it currently has nearly 300 products in development for the US market and 650 products for the international market. The development of these products will be funded through a bigger combined R&D budget, which will reach nearly 500M USD annually. Several other acquisitions in the last three years have also been motivated by size and geographic expansion. These include Teva’s acquisition of Ratiopharm and Cephalon, as well as Cephalon’s acquisition of the Swiss company Mepha.

Moving into Specialty Areas

On the other hand, the rationale behind Sandoz’s acquisition of Fougera Pharmaceuticals is different. In this case, it is less about size and more about the company’s desire to position itself in a clearly defined niche. Fougera Pharmaceuticals’ chief focus is dermatology and it has a very

![Image of Actavis products](image-url)
"...generic pharmaceutical companies are increasingly focused on growing in size, moving into specialty areas and expanding regionally."

strong and established position in the US market. This therapeutic area, although not too large, is dominated by both generic and branded products from a small number of companies. As such, it is almost impossible for a new player to establish itself in this market, other than through acquiring an existing player. India’s Sun Pharmaceutical made a similar move when it acquired Taro Pharmaceutical from Israel in 2011. Both Taro Pharmaceutical and Fougera are considered dominant players in the generic dermatology market.

Expanding Regionally

The consolidation in the generic pharmaceutical industry is also driven by another broader industry phenomenon. The industry has been growing well, with sales growth of global generics industry estimated to be around 10% annually. This is likely to continue into 2012 and 2013. Furthermore, with the impending “patent cliff”, where a number of blockbuster drugs like Pfizer’s Lipitor and Novartis’ Diovana are due to lose their patent protection, generic pharmaceutical manufacturers of similar products will stand to benefit. This is expected to contribute to further growth of the market. However, substantial challenges for generic pharmaceutical companies exist and may become even greater in the future.

Just 10 years ago, the industry’s average annual growth rate was closer to 20%. Now, important and well penetrated markets like the US and Germany grow at less than 10%. Emerging markets are growing at more than 10% annually and therefore it is critical for generic pharmaceutical companies to be well represented in these markets.

Increasingly Competitive Industry

The competitive situation is getting tougher. Typically, after a drug patent expires or when the 6-month exclusivity of the first generic supplier is up, other generic companies will enter the market rapidly. Also, in the US, the desire of many states to better manage their healthcare costs has become a double-edged sword for the generic pharmaceutical industry. On the one hand, there is great interest to promote the use of generic drugs thereby raising demand. On the other hand, there are strong government price pressures on generic products, which will lower overall margins for generic pharmaceutical companies.

A positive development for the generic pharmaceutical industry is that a regulatory path for “biosimilars” is emerging, and companies can benefit from the upcoming patent expirations of biotech drugs. However, it will still be three to five years away before this market segment takes off. In developed markets, only the very large generics manufacturers as well as some pharmaceutical companies are able to offer biosimilars because of the stringent regulatory requirements, high development costs and complex production processes.

Conclusion

Consolidation in the generic pharmaceutical industry will continue unabated. Teva, Sandoz, Mylan and Watson are now big global companies, which have reached a critical mass and are well positioned as a volume player. For medium-sized companies, they will have to work on having well thought out regional strategies, coupled with a unique technology or a well-defined niche focus in specific segments. Examples of regionally focused firms include CFR Pharmaceuticals in Chile, Hikma in Jordan and 3SBio in China. Momenta Pharmaceuticals, a company possessing technology leadership in biosimilars, and Akorn, which focuses on products in ophthalmology, are examples of specialized generics companies. Only through these approaches can these companies generate value for its shareholders, either through greater profits or becoming an attractive acquisition target for larger companies.

About the Author

Adamant Biomedical Investments AG is a Swiss asset manager with exclusive focus on healthcare. It provides services including advisory and portfolio management as well as development of structured investment vehicles. Adamant takes a global research approach, investing in established and emerging healthcare markets worldwide. For more information, please visit www.adamantinvest.com.
Cancer occurs as a result of mutations, or abnormal changes, in the genes responsible for regulating the growth of cells and keeping them healthy. The term "breast cancer" refers to a malignant tumor that has developed from cells in the breast. Usually breast cancer either begins in the cells of the lobules, which are the milk-producing glands, or the ducts, the passages that drain milk from the lobules to the nipple. Less commonly, breast cancer can begin in the stromal tissues, which include the fatty and fibrous connective tissues of the breast.

The Radiological Society of North America (RSNA) 2011 Conference revealed new technology that had been developed for breast cancer tools that demonstrate several methods of technical advancements. These include the Ultrasound, Gamma Camera and Laser techniques for detection of breast cancer.

Statistics

The most common breast cancer statistic you have probably heard is that "1 in 8 women will develop breast cancer in their lifetime." What it should really read is "If everyone lived beyond the age of 70, 1 in 8 of those women would get or have had breast cancer." This statistic is based on everyone in the population living beyond the age of 70. Since breast cancer risk increases with age, the lifetime risk changes depending on age:

- Age 20-29: 1 in 2,000
- Age 30-39: 1 in 229
- Age 40-49: 1 in 68
- Age 50-59: 1 in 37
- Age 60-69: 1 in 26
- Ever: 1 in 8

Breast cancer is by far the most frequent cancer among women with an estimated 1.38 million new cancer cases diagnosed in 2008 (23% of all cancers), and ranks second overall (10.9% of all cancers). It is now the most common cancer both in developed and developing regions of the world (except Japan) and lower (less than 40 per 100,000) in most of the developing regions (Fig. 7a).

Advanced technologies are giving hope to the more than 200,000 women in the United States diagnosed with breast cancer each year. The American Cancer Society's most recent estimates for breast cancer in the United States for 2011 are about 230,480 new cases of invasive breast cancer will be diagnosed in women (Table 1).

The current standard of care for breast cancer screening is x-ray mammography where many pictures from different angles are taken creating a set of images of each breast. In a mammogram, breast tissue appears white and opaque, while fatty tissue appears darker and translucent. X-rays travel unimpeded through soft tissues; however, cancerous tissue absorbs x-rays and can show up on the film as white areas. In a screening mammogram, the breast is x-rayed from center to side.

On the other hand, several factors influence the correct detection of breast cancer, such as age, breast density, hormone replacement therapy, image quality, and experience of the radiologist.

### Different Technologies in Detection of Breast Cancer

From the basic self-exploration or X-Ray screening to the sophisticated stereotactic prone tables or the MRI programs for early detection in groups of women at increased risk, there are several options, each with clinical and economic pros and cons, and classified as either morphological (detect abnormal anatomy) and functional (detect abnormal metabolic activity, often BEFORE anatomical change).

The first Food and Drug Administration (FDA) approved Conventional X-Ray Mammography was in 1969 followed by several techniques and advancement of the breast cancer detection using Computer Aided Detection, Digital Mammography, Digital Tomosynthesis Mammography.
and Diffraction Enhanced Imaging. The advancement of breast cancer diagnosis and screening is growing in different directions including different technologies such as Ultrasound, Gamma Camera and Laser techniques.

Mammography

Mammography is a specific type of imaging that uses a low-dose x-ray system to examine breasts. A mammogram is used to aid in the early detection and diagnosis of breast diseases in women. Imaging with x-rays involves exposing a part of the body to a small dose of ionizing radiation to produce pictures of the inside of the body. X-rays are the oldest and most frequently used form of medical imaging.

Benefits

- Imaging of the breast improves a physician’s ability to detect small tumors.
- The use of screening mammography increases the detection of small abnormal tissue growths confined to the milk ducts in the breast. It is also useful for detecting all types of breast cancer, including invasive ductal and invasive lobular cancer.
- No radiation remains in a patient’s body after an x-ray examination.
- X-rays usually have no side effects in the diagnostic range.

Risks

- There is always a slight chance of cancer from excessive exposure to radiation.
- The effective radiation dose for this procedure varies.
- False Positive Mammograms. 5% to 15% of screening mammograms require more testing such as additional mammograms or ultrasound.
- Women should always inform their physician or x-ray technologist if there is any possibility that they are pregnant.

Ultrasound Imaging

Ultrasound imaging, also called ultrasound scanning or sonography, involves exposing part of the body to high-frequency sound waves to produce images. Ultrasound examinations do not use ionizing radiation (as used in x-rays). Because ultrasound images are captured in real-time, they can show the structure and movement of the body’s internal organs, as well as blood flowing through blood vessels.
Ultrasound imaging is a noninvasive medical test that helps physicians diagnose and treat medical conditions. Ultrasound imaging of the breast produces a picture of the internal structures of the breast.

A new type of ultrasound treatment may help find what traditional mammography has missed. In fact, a study published in 2008 found that adding a screening ultrasound examination to routine mammography revealed 28% more cancers than mammography alone. Recently the FDA approved, Automated Breast Volume Scanner (ABVS) is the world’s first multi-use automated breast volume ultrasound system.

**Benefits**

- Most ultrasound scanning is noninvasive (no needles or injections) and is usually painless.
- Ultrasound is widely available, easy-to-use and less expensive than other imaging methods.
- Ultrasound imaging does not use any ionizing radiation.
- Ultrasound scanning gives a clear picture of soft tissues that do not show up well on x-ray images.
- Ultrasound provides real-time imaging, making it a good tool for guiding minimally invasive procedures such as needle biopsies and needle aspiration.
- Ultrasound imaging can help detect lesions in women with dense breasts.
- Ultrasound may help detect and classify a breast lesion that cannot be interpreted adequately through mammography alone.
- Using ultrasound, physicians are able to determine that many areas of clinical concern are due to normal tissue (such as fat lobules) or benign cysts. For most women 30 years of age and older, a mammogram will be used together with ultrasound. For women under age 30, ultrasound alone is often sufficient to determine whether an area of concern needs a biopsy or not.

**Risks**

- For standard diagnostic ultrasound there are no known harmful effects on humans.
- Interpretation of a breast ultrasound examination may lead to additional procedures such as follow-up ultrasound and/or aspiration or biopsy. Many of the areas thought to be of concern turned out to be non-cancerous only via ultrasound.

**Breast-Specific Gamma Imaging**

Breast-Specific Gamma Imaging (BSGI) is a Molecular Breast Imaging (MBI) procedure that shows the metabolic activity of breast lesions. Small amounts of slightly radioactive substances are injected into the body and special cameras are used to see where they go. Depending on the substance used, different types of abnormalities may be found. Unlike most other imaging tests that are based on changes tumors cause in the body’s structure, nuclear medicine scans depend on changes in tissue metabolism. Due to the higher metabolic activity of cancerous cells, these cells absorb a greater amount of the tracing agent and are revealed as “dark spots.”

**Advantages for BSGI**

- Can find cancers missed by mammography and ultrasound
- Test right in the doctor’s office
- Same-day evaluation
- Accurate results
- Costs less than some other imaging techniques
- May help prevent the need for short term follow up for some patients

BSGI has been performed on more than 200,000 patients in both hospitals and private imaging centers across the USA.
Molecular Breast Imaging

Molecular Breast Imaging (MBI) is a new technology used for breast imaging. MBI identifies tumors in dense breast tissue that are often not visible with X-ray based analog or digital mammography. MBI overcomes a known shortcoming of X-ray mammography. The X-ray breast image is incapable of differentiating between tumors and dense breast tissue. On a mammogram, both appear white. This can make it very challenging for the breast specialist to interpret the image and find potential breast disease. MBI technology is not X-ray based and therefore, has no difficulty in obtaining an image in dense breast tissue.

A small amount of short half-lived radioactive tracer (Tc-99m Sestamibi) is injected into the patient, and within just 10 minutes after injection the scan can begin. During the exam, each breast is lightly compressed between two gamma cameras, with just enough pressure to keep it stationary for 5–10 min while several pictures are taken. MBI provides a better comfort level as only 10 lbs of pressure is used, compared to the 45 lbs of compression needed to take a mammogram.

Positron Emission Mammography

The breast application of the scanner is Positron Emission Mammography (PEM). The scanner uses PET technology to produce tomographic images that allow physicians to visualize breast tumors with an unprecedented resolution of 1.6 mm. In recently published data, PEM has been found to be significantly more precise than existing technologies at identifying benign and cancerous lesions, therefore reducing the number of unnecessary biopsies.

Benefits

- PEM has a higher imaging sensitivity in small tumors <2 cm.
- High spatial resolution (2 mm)
- Short scan time 4–10 minute
- Significantly more precise than existing technologies at identifying benign and cancerous lesions
- 3-D tomographic PET images
- Gentle immobilization (Approx. 50% less force compression than mammography)
- Natural, no compression prone position for improved sensitivity and detection
- Safe and effective with very low tracer dosage
Optical imaging

This test either passes light through the breast or reflects light off it and then measures the light that returns. The technique does not use radiation and does not require breast compression. Optical imaging might be useful at some point for detecting tumors or the blood vessels that supply them.

One example of optical imaging is computed tomography laser mammography (CTLM). This test passes a harmless laser light through the breast tissue and detects large areas of blood vessels that could be a sign of breast tumors. The patient lies comfortably in the prone position with one breast suspended in the scanning aperture. A laser beam sweeps 360 degrees around the breast while the data acquired is processed and reconstructed into Multiplanar and 3D images of the breast. The examination which takes approximately 12 minutes per breast does not require breast compression or an injection.

Benefits
- CT laser breast imaging is part of the emerging field of optical imaging.
- CTLM images blood flow to the breast and thereby should visualize Tumor Angiogenesis.
- CTLM images through implants and dense breast tissue easily.
- The average scan time is about 10-12 minutes per breast.
- No ionizing radiation (no X-ray)
- Dense breasts easily imaged
- Non-invasive/No contrast agent
- Adjunctive to other breast imaging modalities
- No breast compression (comfortable)
- Easy and inexpensive to operate
- High patient throughput

Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) utilizes a magnetic field to visualize the features of soft tissues with highly detailed resolution, even in cases of dense breasts or implants.

During an MRI, like an X-ray, the images are taken of anatomical structures and a contrast media, called Gadolinium, is often injected. This contrast media makes areas of increased blood flow show up as bright spots in the image. Since cancers have increased blood flow, they show up as areas of enhancement. Images of the breast are reconstructed in slices from several different angles.

Unfortunately, not all cancers are visible on MRI and some cancers, such as ductal carcinoma in-situ and lobular carcinoma, are more difficult to detect using MRI. In addition, there are many benign conditions that have increased blood flow and these also enhance under MRI. These enhancements are false-positives and can make treatment planning difficult as well as lead to unnecessary biopsies. One study found that in using MRI in patients with one known cancer, 78% of the additional areas detected were benign at biopsy.

Benefits
- Can image breast implants and ruptures
- Highly sensitive to small abnormalities
- Used effectively in dense breasts
- Can evaluate inverted nipples for evidence of cancer
- Can evaluate the extent of breast cancer
- Can help determine what type of surgery is indicated (lumpectomy or mastectomy)
- May detect breast cancer recurrences and residual tumors after lumpectomy
- Can locate primary tumor in women whose cancer has spread to axillary (armpit) lymph nodes
- Can spot or characterize small abnormalities missed by mammography
- May be useful in screening women at high risk for breast cancer, according to recent studies

Limitations
- Cannot always distinguish between cancerous and non-cancerous abnormalities.
- MRI has historically been unable to effectively image calcifications, tiny calcium deposits that can indicate breast cancer.
• Has been shown to produce a moderate amount of false-positive results.
• MRI is an expensive exam.
• Takes 30–60 minutes compared to 10–20 minutes for screening mammography
• MRI is not nearly as widely available as mammography.
• Requires the use of a contrast agent
• MRI patients must tolerate any claustrophobia
• MRI can be non-specific; often cannot distinguish between cancerous and non-cancerous tumors

• Minimally invasive breast biopsy techniques need to be further developed to evaluate abnormalities detected with MRI

Conclusion
The current technology advancement and future researches are promising for the diagnosis, screening and treatment of breast cancer for early detection with fewer complications and high potential results. In few cases different methods would be required for verification and confirmation for further treatment may be necessary.

Nevertheless, none of the above technology would replace another one; many studies show that in most cases usually two and would more technology would be required in the diagnosis, screening and/or biopsy purposes.

The future exhibits more promising for technology advancement in the breast cancer diagnosis, screening and treatment which would reduce the mortality around the globe.
References


About the Author

Salah Alkhallagi holds PhD in Health Administration from USA, MSc in Medical Electronics and Physics from UK. He is a certified Consultant Engineer (CE) from Saudi Council of Engineers.

He has more than twenty five years of experience in Biomedical Engineering. Dr. Alkhallagi Member of Consultation Group and Liaison Officer of Saudi Food and Drug Authority (SFDA). Medical Device Committee Chairman of the Central Board for Accreditation of Healthcare Institutions (CBAHI). Biomedical Professionals Assessor for Saudi Commission for Health Specialties (SCHS).

A founder member of the Saudi Scientific Society for Biomedical Engineering (SSSBE). Facilities Management and Safety (FMS) working group leader of Joint Commission International Accreditation (JClA). He has participated and presented several papers/presentations at different national/international meetings and training courses.

Dr. Alkhallagi is a member of many associations and organizations such as AAMI, ACCE, ASHE, IEEE, ECRI, ASQ, SQC and SCE.
Mr. Daniel Simon, President & CEO of Heliae Development, LLC, Dr. Jeff OBBARD, Scientific Advisor at Cellana LLC, Mr. Abhiram Seth, Managing Director at Aquagri Processing Pvt Ltd, Dr. Sebastian Thomas, Technical Advisor at Parry Nutraceuticals, Assoc Prof. Lee Yuan Kun, Associate Professor, Department of Microbiology, National University of Singapore (NUS), and Shilpa Ramani, Scientist at Novozymes South Asia are just some of the key experts expected at the 5th Algae World Asia on 7-9 November in Singapore. Together with other industry leaders they will be on hand to analyse recent developments in the algae industry and to discuss the future of the algae sector.

As attention to sustainability and bioenergy escalates among governments and corporations, algae has made its way into the spotlight with the promise of a wide variety of applications ranging from a source of food to feeds, fertilizers and fuel. Algae research has opened doors to diverse possibilities and means to harness the true potential of algae on a commercial scale. Research and development of algae and its supporting technology have come a long way, creating significant changes in the industry, along with an upswing in demand for algaebased products such as astaxanthin.

With that in mind, Conference organizer CMT has drawn up a 2.5 day program agenda that will showcase the advancements in the algae sector, strain collection and maintenance of marine macroalgae, tissue seaweed culture techniques using photobioreactors, biofuel production, and emerging biofertilizer applications in Asia, chiefly Korea, Japan, Indonesia, Malaysia, India, Thailand, Vietnam, and China.

Among the top-notch organizations slated to address country-focussed sessions are:
- Advanced Biomass Research Center Korea
- J-Phoenix Research Inc
- Indonesian Institute of Sciences (LIPI)
- PT Barat Jaya Sentosa Perkasa
- Utar Microalgae
- Aban Infrastructure Pvt Ltd
- Loxley Public Company Limited
- Nong Lam University - Ho Chi Minh City
- Myanmar Spirulina Factory
- Sinopec Research Institute of Petroleum Processing

Adding value to the versatile sessions on commercial production, usage and applications of algae at the 5th Algae World Asia is a separately bookable workshop entitled “Algae Harvesting & Extraction of Bio-Compounds For Production of High Value Ingredients” which runs on 07 November 2012 from 14:00 – 17:00 hrs. The workshop will be conducted by Dr. Chen Shulin, Professor, Department of Biological Systems Engineering, Washington State University. Additionally the summit also presents its delegates with an optional site visit to Biopolis on 09 November 2012 from 14:00 - 16:00 hrs.

More details of the event can be obtained at http://www.cmtevents.com/aboutevent.aspx?ev=121141. Further enquiries on the conference and registrations can be directed to huiyan(at)cmtsp(dot)com.sg or at Tel. 65 63469113
AB Sciex agrees for Sigma-Aldrich® to distribute iChemistry™ solutions

AB Sciex Pte. Ltd, a global leader in life science analytical technologies, announced a distribution agreement with Sigma-Aldrich® to resell the company’s portfolio of mass spectrometry-based tagging chemistries called SCIEX iChemistry™ Solutions. This portfolio of advanced chemistries includes the industry-leading iTRAQ® reagents for proteomics and IDQuant™ standards for pesticide analysis. Sigma-Aldrich will now be able to provide a total solution to mass spectrometry users as well as biologists and chemists who want to start to use mass spectrometry to improve their analyses across a wide range of samples.

SCIEX iChemistry™ Solutions are the industry’s premier reagents and consumables custom designed for mass spectrometry applications. More than 300 peer-reviewed articles about iTRAQ® reagents are in print. The agreement with Sigma-Aldrich is expected to expand the reach of these reagents across the global scientific community as well as make Sigma-Aldrich’s broad portfolio of chemistries more readily available to AB SCIEX’s customer base, which includes thousands of scientists worldwide.

“AB Sciex has unique intellectual property that allows us to develop innovative chemistries that are not available from any other provider,” said Babu Purkayastha, Director of R&D for Consumables at AB Sciex. “By working with Sigma-Aldrich, we are making it easier for scientists to obtain our innovative tagging chemistries as part of a total chemistry solution that can be purchased on Sigma-Aldrich’s website. Sigma-Aldrich’s strength in offering reagents and consumables to biologists, chemists and mass spectrometrists combined with AB Sciex’s chemistries will help make mass spectrometry a de facto standard in bio-analytical science.”

New techniques are necessary if scientists are to answer key biological and analytical questions. Mass spectrometry is a powerful technology for compound detection and quantitation, but scientists around the world are working on assays that require levels of quantitation not possible with even the most sensitive and most robust mass spectrometry instruments. That’s where reagents add value.

The company recently launched Amplifex™ Reagents, the first of a new family of advanced chemistries designed to boost the performance of mass spectrometers, improve data precision and significantly increase sensitivity beyond conventional limits. With the Amplifex™ Reagents, improvements in sensitivity can range from 5x to 1000x, depending on the analyte.
ScienTec Consulting, a leading executive and specialist search, and human resources consulting firm with focus in industries including pharmaceutical, healthcare, medical devices, biomedical sciences, engineering and technology sectors in Asia Pacific, announced its recognition as a Highly Commended winner for the Best Small Recruitment Business and Best Specialist Recruitment Business categories in Asia Pacific.

The honors, announced during The Global Recruiter Asia Pacific Recruitment Industry Awards, were given to outstanding industry players as recruitment has held a crucial place in the economic welfare.

Best Small Recruitment Business finalists with annual turnover within USD 32 million were chosen for their innovation, operational resilience, thorough understanding of candidate and client needs, as well as valuing and nurturing in-house talent. The Best Specialist Recruitment Business category recognizes companies that displayed deep knowledge of their specialized sectors, while offering candidates and end-users added value.

“Gaining recognition for both categories strengthens our focus to provide innovative talent search methodologies, reliable processes and global resourcing capabilities that successfully fulfil our clients’ hiring needs, especially in niche areas where Singapore is still experiencing a talent crunch. I would like to thank our clients for their trust and support,” said Karen Tok, ScienTec’s Managing Director.

“With the increasing competitive landscape, coupled with M&A, corporate reorganization and consolidation initiatives, we certainly see the emergence of new hot skills required in PMETs,” commented Tok.

“Corporate professionals are expected to have a balance of strong business partnering skills in addition to their respective functional expertise. In the fast-changing corporate world, commercial acumen and stakeholder management are essential” she added.

Tok further elaborates, “R&D scientists and engineers, trained regulatory and medical affairs, quality control, project engineers and manufacturing professionals in the upstream or higher value sectors, along with skilled sales and marketing business managers are some of the hot positions that our clients are seeking to fill now.”

ScienTec also revealed the interest of their clients in the medical devices sector and onshore chemical plants and their growth plan in the region. “Singapore is well-poised as the melting pot for an international talent pool, and candidates who have the in-depth knowledge of emerging markets are highly sought after to lead our clients’ expansion plans in Asia Pacific,” Tok concluded.
Agilent Technologies Inc. opened a new Customer Applications and Training Center in South Korea, showcasing its latest bio-analytical instruments. The company’s goal is to collaborate with customers to develop new applications and methodologies for research in the agriculture, environment and semiconductor industries. The center will also help train chemists and engineers in the South Asia and Pacific region on the use of cutting-edge spectroscopy and mass-spectrometry instruments and technologies.

Unique to the center is a clean room designed for engineers, chemists and other scientists in the semiconductor industry to conduct tests and studies of materials using Agilent’s latest atomic and molecular spectroscopy instruments. This Class 1000-certified clean room is maintained to ensure a very low level of environmental pollutants such as dust, airborne microbes, aerosol particles and chemical vapors, specifically less than 1,000 such particles per cubic foot.

“South Korea is an important market for Agilent,” said Dr. Chai-Hock Teng, vice president and general manager of Agilent’s Chemical Analysis Group in South Korea and the South Asia Pacific region. "The country is home to some of the world’s top electronics manufacturers, major Asian and international pharmaceutical and chemical firms, as well as other industrial giants. To better support our customers as they grow and push the boundaries of science, we have established the Agilent Customer Applications and Training Center to offer collaboration and training programs.

“This center is also available to customers outside of South Korea. In fact, we look forward to bringing together customers from the South Asia Pacific region and playing our part in shaping high standards in the agriculture, environment and semiconductor industries.”

The new center enables Agilent’s customers to conduct research and analysis of inorganic materials and compounds in semiconductors, materials science, environment and agriculture.

“This Customer Application and Training Center complements our existing organic and bioscience centers in South Korea,” said Douglas Janson, country operations manager for Agilent’s Chemical Analysis Group in South Korea. “We are responding to our customers’ growing needs for compound identification, greater sensitivity and lower detection limits. The state-of-the-art technologies in the center will help to increase confidence in the results they produce.

“Our customer partnerships help them ensure that agricultural produce and drinking water are safe for consumption or that new compounds can be used safely and effectively in our phones or household appliances. In-depth research will be done to understand them, and rigorous tests will be conducted to ensure their safety and reliability,” explained Janson. “Together, Agilent and South Korea’s scientific community will increase our collaborations and develop new applications that can be deployed throughout Asia and the world.”

The new center has the most advanced Agilent bio-analytical instruments. Through these instruments, scientists can detect, identify and quantify chemicals. In addition to research and collaboration facilities, the new center will offer specialized training programs for scientists, chemists and engineers in South Korea or various Asian markets.

The center is located in the Gangnam area in Seoul and is staffed by a team of experienced chemists and engineers.
Veolia Water Solutions & Technologies appoints new business development director for SEA Engineering Center

Veolia Water Solutions & Technologies (Veolia) is pleased to welcome Carlo Patteri as the new Business Development Director for its Southeast Asia (SEA) Engineering Center. His key responsibility will be to grow the company's business in SEA by providing industrial customers with tailor made water treatment solutions based on Veolia's differentiating technologies.

Carlo joins Veolia with over 10 years of experience in business development, strategic marketing and project management for organizations in the oil & gas, petrochemical, power and water sectors.

Mehbub Khan, General Manager of the Veolia SEA Engineering Center, said, “We are delighted to have Carlo on board to strengthen our presence in Southeast Asia. With a keen understanding of our major industrial markets, he will play an important role in helping our customers understand the value of trusted water and wastewater treatment facilities.”

Carlo shared, “These are exciting times for Veolia in Southeast Asia. Sustainable growth has always been at the heart of everything the company does, and I hope to further reinforce this as we grow in the coming years.”

Carlo holds a Master Degree in Environmental Engineering, and an MBA in Corporate Finance and Strategic Management. He has lived in Asia for seven years.

CLC bio acquires the drug discovery-software company Molegro

CLC bio announced the acquisition of Molegro, a specialized software company focusing on molecular docking, including prediction and analysis of protein-ligand interactions, screening of compound databases for activities against a receptor, and determination of molecule similarity. The acquisition of Molegro supports CLC bio’s strategy of continuously expanding their bioinformatics offerings beyond Next Generation Sequencing, as well as in bioinformatics areas of value to their customer base.

“We have always had a strong focus on the science behind our software, and joining CLC bio allows us to become part of a strong analysis platform and focus even more on developing the next generation of molecular docking products.” says CEO at Molegro, René Thomsen, PhD, and continues, “CLC bio has demonstrated the capability to build an elaborate analysis platform and distribute it internationally, and exactly that competence is the best way to take the features of Molegro’s software to the next level.”

"Since 2005, Molegro has demonstrated the ability to develop and support superior molecular docking products. We look forward to adding the very talented people from Molegro to our team at CLC bio.” states CEO at CLC bio, Thomas Knudsen, and adds, “This acquisition underlines our dedication to always look for the most viable ways to enhance our analysis platform for the benefit of our customers.”

In the coming years, CLC bio will invest significant resources into the continued development of the acquired protein-ligand docking and data modeling software. All existing Molegro customers with an active support and software upgrade contract have been transferred to CLC bio. Effective immediately, Molegro will become part of CLC bio’s organization at their Aarhus, Denmark, headquarters.

“We have always had a strong focus on the science behind our software, and joining CLC bio allows us to become part of a strong analysis platform and focus even more on developing the next generation of molecular docking products.” says CEO at Molegro, René Thomsen.
### OCTOBER 2012

**1 – 2 October**  
2nd Annual Next Generation Sequencing Asia Congress  
Singapore  
Tel: + 65 657 0 2208  
Fax: +65 657 0 2209  
Email: info@oxfordglobalasia.com  
URL: www.ngsasia-congress.com

**1 – 2 October**  
Singapore International Public Health Conference  
Singapore  
Contact Person: Liszt Jimenez (Ms)  
Tel: +65 6593 7868  
Email: phconference@ams.edu.sg  
URL: http://phconference.org/

**3 – 5 October**  
3rd International Conference on Computational Systems-Biology and Bioinformatics  
Bangkok, Thailand  
Contact Person: Kasaporn Sukata  
Tel: +66 2564 6700 ext. 3379-3382  
Fax: +66 2564 6574  
Email: csbio2012@biotec.or.th  
URL: http://www.csbio.org

**7 – 11 October**  
The 12th International Symposium on Dendritic Cells  
Deagu, Korea  
Tel: +82-2-557-8422  
Fax: +82-2-566-6087  
Email: dc@people-x.com  
URL: http://www.dc2012.kr/

**10 – 12 October**  
Bio Pharma- India Today to Future 2020  
Mumbai, India  
Tel: +91 4 60 91 555  
Fax: +91 4 60 91 589  
E-mail: info@fleminggulf.com  
URL: http://www.fleminggulf.com/conferenceview/Bio-Pharma-India---Today-to-Future-2020/274

**15 – 17 October**  
Immunogenicity for Biopharmaceuticals & Biosimilars Asia 2012  
Singapore  
Contact person: Shanice Soh  
Tel: +65 6508 2461  
Fax: +65 6501 2407  
Email: shanice.soh@ibcasia.com.sg  
URL: http://www.immunogenicityasia.com/

**15 – 18 October**  
7th Annual Summit: Branded Generics Strategy Asia  
Singapore  
Tel: +65 6508 2401  
Fax: +65 6508 2407  
Email: register@ibcasia.com.sg  
URL: http://www.generics-asia.com/

**27 – 30 October**  
3rd International Conference on Stem Cells and Cancer (ICSSCC-2012): Proliferation, Differentiation and Apoptosis  
New Delhi, India  
Contact person: Dr. Sheo Mohan Singh  
Email: icsscc2012@gmail.com  
URL: http://www.icsscc.in/

**27 – 31 October**  
Drug Delivery and Formulation Asia Summit 2012  
Shanghai, China  
Contact person: Luke Xia  
Tel: +86-21-5175 7722  
Fax: +86-21-5175 7702  
Email: luke.xia@wtmeg.com  
URL: http://www.ddfasiasummit.com/en/

### NOVEMBER 2012

**1 – 2 November**  
International Conference on SPEECH, IMAGE, BIOMEDICAL & INFORMATION PROCESSING 2012 (SIBIP 2012)  
Punjab, India  
Contact person: Shivani Malhotra  
Email: shivani.malhotra@chitkara.edu.in  
URL: http://sibip2012.chitkara.edu.in

**5 – 7 November**  
Biologics World China 2012  
Shanghai, China  
Tel: +65 6493 2093  
Fax: +604 3823373  
Email: info@imapac.com  

**6 – 8 November**  
LabVietnam 2012  
Hanoi, Vietnam  
Tel: +603 8023 0820  
Fax: +603 8023 0830  
Email: enquiry@ecmi.com.my  
URL: http://www.lab-asia.com/index.php/lab-vietnam

**7 – 8 November**  
4th International Conference on Science & Technology (ICSTIE)  
Penang, Malaysia  
Contact person: Azlina Mohd Mydin  
Tel: +604 3823373  
Fax: +604 3822766  
Email: icstie2012@gmail.com  
URL: http://www.icstie.com

**8 – 9 November**  
5th Algae World Asia  
Singapore  
Contact Person: Sasha  
Fax: +65 63455928  
Email: sasha@cmtp.com.sg  

**12 November**  
Biologics World Taiwan 2012  
Taipei, Taiwan  
Contact Person: Patricia Chong  
Tel: +65 6493 1871  
Fax: +65 6270 2792  
Email: patricia.chong@imapac.com  

**21 – 23 November**  
Singapore International Conference on Dengue and Emerging Infections  
Singapore  
Contact person: Shirley Tay  
Tel: +65 6618 2235  
Fax: +65 6886 8536  
Email: secretariat@events360.com.sg  
URL: http://stopdengue.sg/conference2012/

**24 – 25 November**  
2012 International Conference on Future Bioengineering (ICFB 2012)  
Bangkok, Thailand  
Contact person: Miss Feng  
Email: icfb@cbees.org  
URL: http://www.icfb.org/index.htm

**26 – 27 November**  
BioPharma India Convention 2012  
Mumbai, India  
Contact Person: Huisan Soh  
Tel: +91 4 60 91 555  
Email: huisan.soh@terrapinn.com  
URL: http://www.terrapinn.com/conference/biopharma-india-convention/
27 – 30 November
Pharmaceutical Quality and Compliance Asia Summit 2012
Singapore
Tel: +65 6508 2401
Fax: +65 6508 2407
E-mail: register@ibcasia.com.sg
URL: http://www.pharmaquality-compliance.com

27 – 30 November
Pharma Anti-Counterfeiting & Brand Protection Asia 2012
Singapore
Tel: +65 6508 2401
Fax: +65 6508 2407
E-mail: register@ibcasia.com.sg
URL: http://www.pharmabrandprotection-asia.com

DECEMBER 2012

6 – 7 December
2nd International Conference on Biomedical Engineering and Assistive Technologies
Punjab, India
Contact person: Dr. Dilbag Singh
Tel: +91 98884 92132
Fax: +91 181 2690932/ 2690320
Email: beats2012@nitj.ac.in
URL: http://www.beats2012.org/Beats

12 – 13 December
Biofest 2012, Biotechnology International Conference and Exhibition
Hyderabad, India
Email: biofest2012@brightice.org
URL: http://www.brightice.org

14 – 16 December
International Medical Congress
Phnom Penh, Cambodia
Contact person: Dr Anbin Ezhilan
Tel: +855 092-526647
E-mail: imcui.info@gmail.com
URL: http://imcsensokish.com

22 – 23 December
2012 3rd International Conference on Nanotechnology and Biosensors (ICNB 2012)
Kuala Lumpur, Malaysia
Contact person: Mr. Lee
Email: icnb@cbees.org
URL: http://www.icnb.org/

22 – 23 December
2012 4th Journal Conference on Bioscience, Biochemistry and Bioinformatics (JCBBB 2012 4th)
Kuala Lumpur, Malaysia
E-mail: ijbbb@vip.163.com
URL: http://www.ijbbb.org/jcbbb/4th/

JANUARY 2013

3 – 5 January
Good Clinical Laboratory Practices (GCLP), 2013
Chennai, India
Contact person: Mr. J. Mohanakrishnan, M.Sc / Mr. P. Nandagopal, M.Sc
Tel: 39106800 / 39106803
Email: GCLP@yrgcare.org
URL: http://www.yrgcare.org/gclp/index.php

6 – 7 January
International Conference on Structural and Functional Genomics
Tamilnadu, India
Contact person: Dr.M.Vijayalakshmi
Tel: 04362-264101 (Extn : 678/189)
E-mail: genomics@sastra.edu
URL: http://sastra.edu/icsafg

8 – 9 January
3rd International Conference on Chemical, Biological and Environment Sciences (ICCEBS’2013)
Kuala Lumpur, Malaysia
Contact person: Dr. D. K. Harika
Tel: 04362-264101 (Extn : 678/189)
E-mail: genomics@sastra.edu
URL: http://sastra.edu/icsafg

8 – 10 January
2013 International Congress on Chemical, Biological and Environmental Sciences
Taipei, Taiwan
Contact person: Chandra Nale
Email: icbces@icbces.org
URL: http://www.icbces.org

19 – 20 January
2013 International Conference on Life Science and Technology (ICLST 2013)
Dubai, United Arab Emirates
Contact person: Ms. Yang
E-mail: islct@cbces.org
URL: http://www.iclst.org/

19 – 20 January
2013 International Conference on Scientific Research and Studies (ICRS 2013)
Dubai, United Arab Emirates
Contact person: Jason Wu
Tel: +1-6177166164 (USA, International)
+861-820-777777 (China)
Email: icsrs@sciei.org
URL: http://www.icsrs.org/

25 – 27 January
4th International Conference on Legal Medicine, Medical Negligence and Litigation in Medical Practice
Kerala, India
Contact person: Prof. R.K. Sharma
Tel: 91-11-41586401, 402
Fax: 91-11-41586400
Email:info@dreamztravel.net/dreamztravelindia@yahoo.com/rksharma1@gmail.com
URL: http://www.iamleconf.in

25 – 27th January
2013 Bangkok International Conference on Biological Engineering & Natural Science (BENS’2013)
Bangkok, Thailand
Contact person: Ann Stamp
Email: bens@bbens.org
URL: http://www.bbens.org/

28 – 30 January
BioAsia 2013
Hyderabad, India
Tel: +91 40 6644 6477 / +91 40 6644 6577
Email: info@bioasia.in
URL: http://bioasia.in/2013/

31 January – 2 February
International Conference of Personalized Medicine and Targeted Therapies in Cancer
Sharjah, United Arab Emirates
Contact person: Sujatha Kristensen
Tel: 971 4 4270492
Fax: 971 4 4270493
Email: pco@pmtc2013.com
URL: http://pmtc2013.com/index.html
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