A Crisis in the Development of Antibiotics

Bacterial Culture and Anti-microbial Susceptibility Testing
– their Use in Guiding Therapy

Epidemiology and Impact of Multi-Drug Resistant Gram Negative Infections in Critically Ill Patients in Asia

Antibiotics and Resistance in Ocular Infections
– Indian Perspective
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CONFERENCE CALENDAR
EDITORIAL

Antibiotics—Still Fighting the Good Fight

Virtually everyone has either had the experience of becoming ill with an infection, themselves or often for their child and the doctor prescribing an antibiotic for resolution of the condition. In fact, we essentially expect that virtually any infection will be quickly cured with an antibiotic. Expectations are that when a new infection is found as has happened many times in the last few years, it will also submit to our present inventory of antibiotics or a new antibiotic will quickly be available. However, there have been some serious concerns about that scenario. These concerns originate from several sources. The most important is the emergence of antibiotic resistance bacteria and the diminished pipeline of development of new antibiotics.

In current news, NDM1 (found in India 2010), antibiotic resistant pneumonia as well as the continued problems with various types of gram negative bacteria rapidly becoming antibiotic resistant increases the concerns about these strains. More than 20 years ago, it was found that some strains of Staphylococcus aureus developed antibiotic resistance and came to be known as MRSAs, methicillin resistant Staphylococcus aureus. This type of bacteria was at first largely found in hospitals but these organisms are now found in the community and although susceptible to some antibiotics, these infections lead to many additional hospital days and heightened costs. An antibiotic developed to deal with MRSAs, vancomycin, has not lived up to this promise and has itself shown resistance in a form of organism known as VRSA, vancomycin resistant Staphylococcus aureus. However, slowly new antibiotics are being developed, but resistance adds markedly to human suffering and health care costs.

Adding to the problem of resistance has been our overuse of antibiotics which are still largely seen as ‘wonder drugs’. However, we now understand that unlimited use of antibiotics only adds to the problems of the development of resistance, encouraging the emergence of “superbugs” that cause significant problems with our ability to deal with them. Europe has added another dimension to the problem of resistance with the development of resistant fungal disease which has been suggested to be related to the large amount of cheeses which are protected by chemical relatives of the antifungals used to treat infections. The growing aging population, people with reduced immune responses— as a result of some disease or treatment, such as chemotherapy— and increased international travel has increased the world-wide concern for adequate drugs to fight infectious diseases from bacteria and fungus.

Viral infections are not included in this analysis as antivirals are a separate class and are not considered in this analysis as antibiotics and antifungals usually do not have effective therapeutic action against viruses.
The solution seems obvious: develop new antibiotics and that certainly seems to be what is expected. However, as it turns out that there has been a significant crisis in the development of new antibiotics as the developmental pipeline has slowed down for over a decade or more. Reasons for this are several, but the increasing antibiotic resistance means that after years of effort necessary to have a new antibiotic approved by the FDA, the therapeutic becomes ineffective, thereby, decreasing the returns. Also, the work to develop new antibiotics has not been as effective as planned. Antibiotics are largely derived from natural sources, often fungus, and the process of isolating and screening potential antibiotics requires time and considerable funding. The big pharmaceutical companies have left this work for small companies and academic institutions. However, some of this effort is now beginning to yield results and there is renewed effort in antibiotic development.

Antibiotics have a special meaning for Southeast Asia as the warm, humid environment allows bacteria and fungus to thrive. Human suffering in terms of loss of life, illnesses and disabilities such as blindness as the outcome of infections is very serious. Development of better antibiotics and antifungals, in particular, should be a healthcare priority for nations in this region.

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AUSTRALIA

Deadly Mosquito Virus on Rise in Australia

Cases of a deadly mosquito-borne virus increased dramatically in Australia last year, with further outbreaks possible. Three people died and there were 16 confirmed cases of Murray Valley encephalitis virus in 2011, according to an article in the Medical Journal of Australia.

There were no cases reported in 2010 and just four confirmed cases of the virus in 2009, data from the National Notifiable Diseases Surveillance System shows.

The virus is endemic in northern Australia but re-emerged in southeastern Australia last year, according to author Dr Jack Richards, of the Victorian Infectious Disease Service at Royal Melbourne Hospital, and his co-authors.

The increase in cases came in the wake of significant regional flooding, with deaths occurring in Western Australia, South Australia and the Northern Territory. “The risk during this summer and the coming autumn remains uncertain, especially in areas that remain flooded,” the report said.

“Recent circumstances remind us of the limited information we have about this disease, the challenges of clinical management and the need to prepare for future outbreaks.” The virus, which causes brain inflammation, is fatal in about 15 to 30 per cent of cases, with long-term neurological problems occurring in 30 to 50 per cent of survivors. Just 40 per cent of sufferers make a complete recovery. Symptoms include fever and headache, lethargy, confusion and sometimes seizures. There is no cure and no vaccine.

The researchers said they are eagerly awaiting further trial data on interventions and the future development of effective antiviral agents. In the meantime, prevention relies on the use of sentinel chicken flocks – whose sera are tested regularly to provide an early warning of virus activity – and on mosquito control.

People are advised to use insect repellents and wear long and loose clothing to help reduce mosquito bites.

Hope for Ovarian Cancer Diagnosis

Australian scientists are one step closer to improving the diagnosis of ovarian cancer, which is infamous for spreading quickly and being difficult to detect.

A team from Sydney’s Garvan Institute of Medical Research has been comparing tumour samples from ovarian cancer patients to tissue samples from normal ovaries since 2008. By scanning the genome, the team has been able to pinpoint changes in the DNA of six specific genes, which they believe could be used to identify ovarian cancer. Scientists hope the findings, which were published in the journal Cancer Letters, could one day lead to earlier diagnosis.

‘In the future high-risk patients, such as post-menopausal women, would actually be able to go in for a yearly blood test and we would be able to pick up these changes in the DNA,’ researcher Brian Gloss said. ‘The idea would be that on a screening basis we would be able to pick up early disease before it spreads.’

Mr Gloss said the biggest problem with the gynaecological disease, which is the seventh most common cause of cancer death in Australian women, was that it was very difficult to spot, with ubiquitous symptoms that include bloating or abdominal pain. Once it has invaded the pelvis and other organs, including the stomach, bowel and lungs, it is often very difficult to treat. ‘We haven’t been able to improve significantly on the survival of ovarian cancer patients for a while,’ he said.

The findings will now materialise in general practice for some time, but Mr Gloss said he hoped the team could expand the study and eventually begin clinical trials.
Malaria Decloaked

Researchers at the Walter and Eliza Hall Institute have identified a molecule that helps the malaria virus hide from the immune system. The malaria parasite could soon find it a lot harder to hide from the immune system now that researchers from the Walter and Eliza Hall Institute have discovered a key molecule that acts like a 'cloak of invisibility.'

In research published in the journal Cell Host and Microbe, Professor Alan Cowman from the institute's Infection and Immunity division and colleagues reveal details about the first molecule found to control the genetic expression of PfEMP1 (Plasmodium falciparum erythrocyte membrane protein 1), a protein that is known to be a major cause of disease during malaria infection.

"The molecule that we discovered, named PfSET10, plays an important role in the genetic control of PfEMP1; an essential parasite protein that is used during specific stages of parasite development for its survival," Professor Cowman said.

It is also responsible for helping the parasite to escape destruction by the immune system, by varying the genetic code of the PfEMP1 protein so that at least some of the parasites will evade detection.

This variation lends the parasite the 'cloak of invisibility' which makes it difficult for the immune system to detect parasite-infected cells, and is part of the reason a vaccine has remained elusive.

Professor Cowman said identification of the PfSET10 molecule was the first step towards unveiling the way in which the parasite uses PfEMP1 as an invisibility cloak to hide itself from the immune system.

"As we better understand the systems that control how the PfEMP1 protein is encoded and produced by the parasite, including the molecules that are involved in controlling the process, we will be able to produce targeted treatments that would be more effective in preventing malaria infection in the approximately three billion people who are at risk of contracting malaria worldwide," he said.

Eye Contact Helps Detect Autism

Unusual patterns of eye contact could help detect developing autism symptoms in babies just six months old, reveals a study. La Trobe University psychologist Kristelle Hudry, a key researcher in the study, says the results of the study are linked with emerging autism. Hudry and her UK colleagues studied six to 10-month-old babies who were at risk of developing autism because they had a sibling with the condition, the journal Current Biology reported.

They placed sensors on the babies' scalps to register their brain activity, while they viewed videos of faces that switched from looking at them to looking away, or vice versa, said a university statement. "These results are important because early diagnosis can secure the best possible outcome for individuals with autism spectrum disorders (ASD), through early access to intervention," Hudry said.

While behaviours characteristic of autism emerge over the first few years of life, a firm diagnosis using existing methods can usually only be made after the age of two.

In reality, however, diagnosis often doesn't happen until much later, so most autism research has concentrated on children older than two years, which means we still know very little about the very earliest symptoms and signs, said Hudry.

Releasing the report in the UK, Mark Johnson, professor and chief investigator, University of London, said: "Our findings demonstrate for the first time that direct measures of brain functioning during the first year of life associate with a later diagnosis of autism - well before the emergence of behavioural symptoms."
Simple Hair Test to Find Breast Cancer

Hair test to screen for breast cancer is being developed by an Australian company, which says it could become a viable alternative to mammography.

SBC Research is conducting an 80-patient trial to test its hypothesis that women with breast cancer have higher levels of phospholipids in their bloodstream that can be detected in their hair.

The company aims to commercialise the test and says it could be made available to women of all ages as an initial screening, unlike mammography which is largely restricted to women over 50.

Those involved in the consortium began developing a test based on their discovery that hair from women with breast cancer had a different cell structure to hair from other women.

They used synchrotron X-ray technology to detect 70 per cent of women who had breast cancer in a series of trials, by observing a ring in their hair not present in disease-free hair.

But researchers are now taking a different approach that they believe will deliver a more accurate test.

They made the lipid discovery when researcher Dharmica Mistry noticed her hair developed a ring, despite being a clear negative for breast cancer.

"I was looking at X-ray diffraction patterns of hair and I used to use my hair as a regular control," she said. "The only thing I did differently was using olive oil in my hair every now and then. I stopped using it and the feature disappeared."

"That led to a series of experiments to assess if what we were seeing was lipid in nature. The hypothesis is that the tumour causes increased lipids in the patient, which is released into the bloodstream and incorporated into the hair fibre."

Chief scientist Peter French said there was evidence to show increased lipid content in the membranes for cancer cells compared with normal tissue. "Cell membranes are comprised of lipids, and what appears to happen in breast cancer is that there is increased fluidity of those lipids. We think that's why cancer is able to invade."

Ms Mistry said the test required her to extract internal lipids from hair, rather than any secretions or products on its surface.

"I grind the hair, put it in a vial with an extraction solvent and shake it around to extract the lipids from the fibre." The resulting liquid was then analysed to determine its lipid content.

The hair test is among 49 Australian entries for funding from a $100 million global research and development challenge by the company GE, which aims to accelerate innovations in breast cancer.

Mr French said a larger second study was needed to confirm the accuracy of the hair test, but results were encouraging. The test was “probably a year or two away” from being commercially available.
CHINA

Fatal Bird Flu Can't Spread Between Humans

The strain of bird flu that killed a Chinese man cannot spread among people, a health agency said, appealing for calm after the country's first reported case of the disease in humans in 18 months.

Genetic analysis indicated the virus spread directly from poultry to the victim, who died in the southern city of Shenzhen, the Shenzhen Disease Control Center said in a statement reported by the official Xinhua News Agency.

“Though it is highly pathogenic to human beings, the virus cannot spread among people,” the statement said, according to Xinhua. “There is no need for Shenzhen citizens to panic.”

H5N1 rarely infects humans and usually only those who come into close contact with diseased poultry. Scientists are closely watching the virus for any signs it is becoming more easily transmissible from human to human.

Xinhua said health authorities still were trying to figure out where he was infected. The Guangdong health department has said 120 people who had close contact with the infected victim have not developed any abnormal symptoms.

The World Health Organization says globally 336 people have died from 573 confirmed bird flu cases since 2003. Of these, 40 cases were in China, 26 of which were fatal. His death was a week after two dead birds tested positive for the virus in Hong Kong, which is just across a river from Shenzhen.

More than 19,000 birds at a Hong Kong market were slaughtered and imports and sales of live poultry were banned for three weeks after a chicken carcass tested positive for H5N1. Lab tests later confirmed that an Oriental magpie robin found dead on Dec. 17, 2011 was also infected.

China's last reported human case of H5N1 was in June 2010. A pregnant 22-year-old woman from central Hubei province died after being exposed to sick and dead poultry.

China to Monitor Radiation in Water Around N-Plants

China's health authorities have been told to check for radiation in drinking water around the country's nuclear power plants.

The monitoring will cover areas within 30 km of plants that are both in operation and under construction, according to a national working plan for drinking water monitoring in 2012, which was published on the website of the Ministry of Health Tuesday.

The document also specified that the plants will include the Tianwan nuclear power plant in Jiangsu province, Qinshan plant in Zhejiang, Daya Bay and Ling’ao nuclear power stations in Guangdong, as well as those under construction in Zhejiang, Liaoning, Fujian, Shandong, Guangdong, Guangxi and Hainan provinces, said Xinhua.

The plan asked the authorities to consider both natural radiation conditions and artificial radioactive matters that may have leaked from the nuclear power plants.
China has approved the world's first hepatitis E virus (HEV) vaccine, said China's Ministry of Science and Technology.

HEV is transmitted via the fecal-oral route, by consuming contaminated water or food. In China, HEV is the most common type of hepatitis but no commercially available vaccine previously existed, said the World Health Organization.

The HEV 239 vaccine, sold under the trade name Hecolin™, was developed by a team of researchers from Xiamen University and Xiamen Innovax Biotech Co. Ltd. in China's Fujian province. After 2005, the Chinese National High-tech R&D Program (863 program) began to sponsor the research.

The recombinant vaccine is prepared using virus-like particles (VLPs) of the HEV structural protein, and administered intramuscularly as three separate doses, with the second and third dose given 1 months and 6 months after the first dose.

Results of a Phase III trial involving 97,356 healthy participants aged 16 to 65 years in China's Jiangsu province were published in The Lancet in August 2010. Half of the participants were given the vaccine, while the other half received a placebo. In the year following the receipt of the third dose, 15 participants in the placebo group developed hepatitis E compared with none in the vaccine group, with vaccine efficacy after three doses reported as 100 percent.

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Two China scientists have been awarded a prestigious US prize for their groundbreaking work with a form of leukemia. By combining traditional Chinese medicine and western approaches, they increased the five-year survival rate of acute promyelocytic leukemia (APL) from 25% to an astonishing 95%. In recognition of their contribution, Drs. Zhen-Yi Wang and Zhu Chen were named recipients of the 7th Szent-Györgyi Prize for Progress in Cancer Research by the National Foundation for Cancer Research in the US. In the early 1980s, Dr. Wang was a clinical researcher at the Ruijin Hospital in Shanghai. He performed the first successful induction therapy on APL patients using all-trans retinoic acid (ATRA). The use of ATRA produced a significant increase in survival rates.

Dr. Chen, who had been one of Wang’s Master’s students, added a TCM to the mix. Dr. Chen helped to identify the molecular mechanisms of both ATRA and arsenic trioxide, a TCM that had been in use for 2,400 years, on APL. Starting in the 1990s, Drs. Wang and Chen together conducted clinical trials combining ATRA and arsenic trioxide in patients with APL, the current standard of care. APL is a subtype of acute myelogenous leukemia (AML), a cancer of the blood and bone marrow, representing about 5% to 8% of all cases of AML. Median age of onset for the disease is 40, which is much younger than other forms of AML, about 70. Its incidence is higher in people of Latin American origin.

Dr. Wang is currently Professor Emeritus at the Medical School of Shanghai Jiao Tong University and is recognized as the one of the first experts in thrombosis and hemostasis in China. He published 320 scientific papers during his distinguished career. In the past, Dr. Wang served as honorary editor-in-chief of The Chinese Journal of Hematology, and former council member of International Society for Heart Research and International Society on Thrombosis and Haemostasis (ISTH).

Dr. Chen is the current Minister of Health for the Peoples Republic of China, a position he has held since 2007. Dr. Chen is the only non-party member to hold that post since the 1970s. Sent to the countryside for “re-education” during the Cultural Revolution, Dr. Chen learned medicine on his own for two years. He was a “barefoot doctor” practicing many of the traditional Chinese therapies. Recognized for his medical work by the local rural population, Dr. Chen was selected to attend medical school at Shangrao Health School Jiangxi. He later received his Master’s degree from the Shanghai Second Medical University and his Doctorate from the University of Paris VII.

The Szent-Györgyi Prize includes a $25,000 honorarium. An official ceremony will be held on March 6, 2012 in New York City to award the Prize to Dr. Wang and Dr. Chen.

“Drs. Wang and Chen have quite literally changed the face of medicine for those patients suffering from APL. Their combined work has saved millions of lives around the world both today and for future generations,” said Dr. Beatrice Mintz, Fox Chase Cancer Center, Chair of the 7th Selection Committee of Szent-Györgyi Prize and winner of the 6th Annual Albert Szent-Györgyi Prize. “I cannot imagine a better testament to the outcomes of investing in cancer research than what these two distinguished scientists have achieved.”

“In keeping with the spirit of nonconformity that NFCR founder Albert Szent-Györgyi is known for, the selection of Drs. Wang and Chen has a significant meaning to those who work in the trenches of cancer research each day,” said Sujuan Ba, Ph.D., Co-Chair of the Szent-Györgyi Prize Selection Committee and Chief Operating Officer of NFCR. “True scientific discovery comes from ideas and basic research. These two scientists are inspirational as they both have dedicated their lives to this work that will impact the world for generations to come.”

“I am so glad to see that the efforts we have devoted to research on Leukemia these last several decades have led to solid clinical benefits to APL patients around world. We will continue our efforts in finding more effective therapies to treat cancers,” said Dr. Wang.

“It is quite humbling to know that our colleagues across the various scientific disciplines selected us. We know there are thousands of scientists worldwide working every day to cure cancer. I hope our work may continue to inspire others,” said Dr. Chen. “This is a great honor for Dr. Wang and me.”
Around half a million newborns in India suffer from congenital genetic disorders every year - the highest in the world - but advances like molecular pathology have helped detecting these disorders at early stages, an expert said.

"The number of children born with genetic disorders in India is highest in the world," I.C. Verma, director, Sir Ganga Ram hospital, said at International Symposium on Molecular Pathology.

However, because of advancements like molecular pathology, the cases of genetic disorders are being detected at an early stage, he said.

"There has been an increase in prenatal diagnosis in such cases and its success is above 30 percent," Verma claimed.

Molecular pathology is a discipline within pathology which focuses on the study and diagnosis of disease through the examination of molecules within organs, tissues or bodily fluids.

Indian Basil, popularly known as Tulsi, can be used effectively in treating patients who are exposed to radiation according to scientists at the Defense Research and Development Organization (DRDO).

The scientists are developing a herbal medicine based on the plant and will be conducting the second phase of trials to test the effectiveness of the medicine.

According to the scientists at DRDO, tulsi contains anti-oxidant properties that not only negates the ill effects of radiation, but can also be used among patients who undergo chemotherapy for cancer.

Speaking to the press, DRDO’s chief controller (R&tD) W Selvamurthy said that the project cost around Rs 7 crore and added that the medicine could be commercially available in the near future. “Tulsi-based medicine is already in second phase of clinical trials. It has to undergo some more trials before it is finalized and goes for commercial production. Animal trials have also been conducted and their results were quite encouraging”, he said.
A new variety of corn that is suitable for organic and biological farming systems could benefit New Zealand farmers who rely on corn seed imports.

A new corn hybrid developed by Blue River Hybrids has been shown to protect corn from pollen drift including GMO pollen. The corn called PuraMaize has been developed through selective traditional parent - line breeding of corn plants which are able to block pollen from other varieties. This gene blocking mechanism is found mainly in tropical corn plant species.

New Zealand farming sector has a zero-tolerance policy for commercial GE crops. This stand supports our clean green and safe food reputation, but in the last decade farmers have experienced a number of instances of GE contamination of corn seed, which have harmed farmers and threatened exports. The corn variety gives farmers a solution in the fight against deliberate or accidental contamination of the food supply by GE constructs.

“This is a welcome development. The new variety has good yields and if grown organically has no chemicals. This is in stark contrast to GE grown crops which have unstable yields, are laden with insecticidal toxins and heavily sprayed with herbicides that affect reproduction and the endocrine system,” says Claire Bleakley, president of GE-Free NZ in food and environment.

In Africa there are many varieties of corn that have been developed through traditional breeding to withstand droughts and pests, yet instead of focusing on the sustainable traditional varieties Agri-biotech see companies are pirating these communal traits then adding their patented genes and claiming the benefits.

The handful of GE food crops approved for commercialisation - corn, soy, canola, cottonseed, sugar beets, sugar, potatoes - are mostly now engineered with insecticidal genes and herbicide resistance genes so they can be sprayed through their growth with a cocktail of herbicides like RoundupReady, Busta, 2,4-D, and Targa.

In stark contrast to non-GE food plants that cannot withstand herbicides while growing, GE varieties survive and absorb the pesticides, increasing the exposure of consumers to chemicals that are known to be toxic.

“Importers of seed must take care to stay within the law and it is incumbent on them to seek varieties that can give farmers assurance that they are growing seed that is uncontaminated with GE” said Mrs Bleakley.
SINGAPORE

Derivatives from a Common Edible Southeast Asian Fruit, Mangosteen, are being Examined as Potential New Antibiotics

The health care crisis in the development of new antibiotics has reached worldwide dimensions and many academic and small companies are involved in the race to bring a new antibiotic for patient use. The pharmaceutical industry since the seminal finding of penicillin, has relied on screening natural products derived mostly from various types of fungus for succeeding generations of antibiotics. Mangosteen (Garcinia mangostana) is a tropical plant from South East Asia, India and Sri Lanka with a long history of use as a traditional medical plant for the treatment of chronic diarrhea, infected wounds, skin infections and dysentery. Research efforts to find useful new derivatives of this plant have intensified with the identification of major bioactive secondary metabolites of mangosteen such as the xanthone derivatives, which display potent pharmacological activities including antibacterial, antifungal, antioxidant, anti-tumoral, anti-inflammatory and anti-allergy properties. One of these derivatives is alpha-mangostin, which has demonstrated bactericidal activity in vitro against gram positive bacteria including \textit{S. aureus} and MRSA. These findings suggest that alpha-mangostin has potential for the treatment of MRSA infections; however, developing new molecules is a difficult and risky business as there are essentially an unlimited number of possible modifications and the standards for new antibiotics are high.

Scientists from the Singapore Eye Research Institute and their colleagues at the Bioinformatics Institute of Singapore and Nanyang Technological Institute have made progress in understanding how the alpha-mangostin derivative works to disrupt the bacteria membrane which paved the way for new modifications. It has also been found that alpha mangostin has outstanding killing action on one of the most deadly bacteria, the methicillin-resistant \textit{Staphylococcus aureus}, which has become a major focus for the development of new antibiotics. This type of bacteria is often found in hospitals and shows significant mortality world-wide. It is hoped that this fundamental understanding of the mechanism of action will be useful for more rapid progress towards better antibiotics to fight these deadly infections.

OTHER REGIONS

New Lung Cancer Test Predicts Survival

Clinical trials in the United States and China have shown that a new gene-based test for patients with lung cancer beats standard methods in predicting survival, researchers reported.

The findings, published in the British medical journal, The Lancet, should help doctors to make more accurate prognoses and better choices for treatment, the scientists said.

Lung cancer is the most lethal type of the disease worldwide, claiming some 1.4 million lives – more than breast, colon and prostate cancers combined - each year.

The experimental test measures the activity of fourteen genes within cancerous tissue, and is especially effective is assessing a form called non-squamous non-small cell cancer, commonly brought on by tobacco use. "This has the potential to help hundreds of thousands of people every year to survive longer," said David Jablons, the main architect of the study and a professor at the University of California in San Francisco (UCSF).

Currently, doctors classify early-stage lung cancers by their size, location and microscopic profile. Known as staging, this type of assessment guides decisions on the use of supplementary treatment - including chemotherapy - after cancerous tissue is removed. A more precise prognosis would mean "more people who might benefit from additional therapy could receive it after surgery, before any residual cancer has had a chance to grow," Jablons explained in a statement.

Previous research has shown that chemotherapy given in early-stage lung cancer helps thwart recurrence when there is evidence of lymph node involvement. The problem, however, is that this especially insidious form of the disease is hard to spot early on.

Only some 30 percent of patients in the United States, for example, are detected in the earliest stage, and even then survival is far from guaranteed – 35 to 45 percent of patients identified with Stage One lung cancer die within five years. "The prognostic test would address the inability to identify these patients," Jablons said.

In the US trial, the new testing method - designed at UCSF and developed by the California-based company Pinpoint Genomics - used an algorithm to calculate the risk of death after examining the tissue of 361 patients at the UCSF Medical Centre as low, medium or high. All of these patients had had surgery to treat non-squamous, non-cell lung cancer. The algorithm was then applied to 433 other patients with the earliest stage of the same type of cancer, and their survival rate was monitored over five years. The method accurately identified patients with high, intermediate and low risks of death, the researchers said. A similar study in China, conducted by the China Clinical Trials Consortium, confirmed the results. A disclosure notice in The Lancet notes that Jablons and several of the co-authors have paid consultant relationships with Pinpoint Genomics.
Study Confirms Groundbreaking Advance in Stem Cells

The first use of embryonic stem cells in humans eased a degenerative form of blindness in two volunteers and showed no signs of any adverse effects, according to a study published by The Lancet.

Publication in the peer-reviewed journal marks an important step for embryonic stem cells, which were hailed as a miracle cure after they were discovered in 1998 but then ran into technical and political hurdles.

The results of the cautious first-stage test, designed to evaluate whether the treatment is safe, had been previously announced by Massachusetts biotech firm Advanced Cell Technology (ACT) Inc. The positive outcome in the United States opened the way to the first trials in Europe. Embryonic stem cells are extraordinarily versatile cells, that can differentiate into any tissue of the body. Scientists have been hoping to turn them into replacement for tissue lost through disease or other safety concerns emerged and both patients recovered a little vision, although this was not the point of the test.

At the outset, the older patient was able to read 21 letters on a standard chart of visual acuity. This rose to 33 letters after two weeks before settling at a stable ability to read 28 letters, the study said. The woman with Stargardt's disease, a former graphic artist, at first could only see hand movements, but this improved after the transplant to being able to see single fingers and to reading five letters of the alphabet. "However, that doesn't really capture the difference it has made in their life," Bob Lanza, ACT's chief scientific officer, said in an email to AFP.

"The Stargardt's patient reports that she can see more colour and has better contrast and dark adaptation out of the operated eye. In fact, she started using her computer and could even read her watch... (and) says she can even thread a needle now."

Lanza noted that the improvements occurred in patients who were already at a very advanced state of the disease, so the trials were encouraging for patients at an earlier stage of degeneration.

Clinical trials of novel drugs or treatments typically undergo a three-phase process, enrolling a progressively larger number of patients, to make sure they are firstly safe and, secondly, effective.

Twelve patients with Stargardt's have been cleared by British medical authorities to undergo transplant, with progressively higher doses of cells, at the Moorfields Eye Hospital in London.

Brain ‘Hears’ from Different Location than Earlier Thought

Now hear this! The part of the brain used for speech processing is in a different location than originally believed, according to a US study Monday that researchers said will require a rewrite of medical texts.

Wernicke's area, named after the German neurologist who proposed it in the late 1800s, was long believed to be at the back of the brain's cerebral cortex, behind the auditory cortex which receives sounds.

But a review by scientists at Georgetown University Medical Center of more than 100 imaging studies has shown it is actually three centimeters closer to the front of the brain, and is in front of the auditory cortex, not behind.

"Textbooks will now have to be rewritten," said neuroscience professor Josef Rauschecker, lead author of the study which appears in the Proceedings of the National Academy of Sciences. "We gave old theories that have long hung a knockout punch. Rauschecker and colleagues based their research on 115 previous peer-reviewed studies that investigated speech perception and used brain imaging scans -- either MRI (functional magnetic resonance imaging) or PET (positron emission tomography).

An analysis of the brain imaging coordinates in those studies pointed to the new location for Wernicke's area, offering new insight for patients suffering from brain damage or stroke. "If a patient can't speak, or understand speech, we now have a good clue as to where damage has occurred," said Rauschecker. It also adds an intriguing wrinkle to the origins of language in humans and primates, who have also been shown to process audible speech in the same region of the brain. "This finding suggests the architecture and processing between the two species is more similar than many people thought." Lead author Iain DeWitt, a PhD candidate in Georgetown's Interdisciplinary Program in Neuroscience, said the study confirms what others have found since brain imaging began in earnest in the 1990s, though some debate has persisted.

"The majority of imagers, however, were reluctant to overturn a century of prior understanding on account of what was then a relatively new methodology," he said.

"The point of our paper is to force a reconciliation between the data and theory."
A Crisis in the Development of Antibiotics

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When the first antibiotic, penicillin, was discovered (some say rediscovered) by Alexander Fleming who received the Nobel Prize in 1928 for the achievement, it was indeed an incredible event as the balance of morbidity from infections was quickly shifted toward recovery rather than death. The name originated from the source, a mold named Penicillium (Figure 1), and indeed natural sources are still an important source of new antibiotics (see BioBoard for a SE Asian fruit—Mangosteen— that is being investigated as a source of new anti-microbials). In healthcare systems world-wide, most patients assume that there will be an antibiotic available to fight whatever infection they might have contacted. However, for a number of reasons some serious issues have been met with in the advancement of new antibiotics which have slowed their development, especially at a time when many bacteria are not affected by some of the existing antibiotics and new forms of common bacteria have emerged that find ways of changing their biological activity so that antibiotics lose their potency.

Causes for Antibiotic Resistance

The list of antibiotics is extensive, but issues complicating their use, such as harmful side-effects, specificity in their action, has resulted in limitations in their use and more importantly, the overuse of antibiotics has led to problems affecting their development. Overuse has become a major factor in the development of what is widely known as “antibiotic resistance” resulting in hesitation by the pharmaceutical industry to put effort into discovering or synthesizing new antibiotics resulting in a diminished pipeline of new drugs (Table 1). The term “antibiotic resistance” is fairly common in both the public press and it has been the subject of numerous news reports as well as many scientific papers (1–4). So what exactly is antibiotic resistance and why is it such an issue?

Table 1. This table represents the profile for major classes of antibiotics. Dates largely represent the times that primary members of a class of antibiotics was approved except for penicillin which was discovered in 1928 but not approved until 1940.
Antibiotic resistance has a genetic basis and from an evolutionary view, bacteria has always had the potential for resistance, but the widespread use of antibiotics in healthcare, food preservation and for animal use has provided the opportunity for resistance to become operational by selecting for bacteria expressing mutated genes (2). As bacteria are hardy organisms, the mutated genes can be shared between bacteria increasing the spread of resistance. It is important to note that resistance in this sense has been an issue mainly for bacteria, but more recently resistance has been recognized for fungal infections as well (5). There are many different types of antibiotics (Table 1), some have very specific action while others are termed broad spectrum, killing both Gram Positive and Gram negative bacteria. When bacteria develops resistance one or more antibiotics may become ineffective and these bacteria are termed “superbugs” and of course, it is more difficult to overcome the infection. Confounding factors are the fact that patients overuse antibiotics, doctors frequently overprescribe their use and in some countries, antibiotics can be readily purchased over the counter (2). The medical community is actively attempting to limit the use of antibiotics to situation where they are clearly needed. In fact, many patients assume that any type of infection can be killed by antibiotics; however, many infections such as the common cold are viral in nature and antibiotics have no effect on viruses. When antibiotics are tested for their effectiveness on bacteria, a common method used in the pathology and microbiology laboratory is the Minimal Inhibitory Concentration, MIC value which is often expressed in amount per volume, such as ug/ml. Note that the MIC value is for growth inhibition not actual killing. If, as happens, bacteria normally have a MIC value for penicillin of 1-2ug/ml and when resistance occurs this value may increase by more than four times. In the laboratory, we can simulate the selective pressure of the overuse of antibiotics by constantly exposing an organism to an antibiotic and then testing to determine if the MIC value changes. An example of this method is seen in Fig. 2. In this example, a standard strain of Pseudomonas was tested for the ability to develop resistance to two different current antibiotics, gentamicin and norfloxacin. Both of these antibiotics showed signs of developing resistance by the increase in MIC values. However, the push in current new antimicrobial research is to develop drugs to which bacteria do not easily develop resistance. As seen at the bottom of Fig. 2, SERI-B2 which has been designed and synthesized at the Singapore Eye Research Institute as a new antibiotic did not show resistance (resistance is defined as more than a 4-fold increase in MIC). It is easy to extrapolate this laboratory example to the real world where many thousands of patients are taking antibiotics with the ensuing development of resistance.

Emergence of Multi-drug Resistance Bacteria

As bacteria are small organisms they thrive in enormously large numbers and they multiply rapidly. Thus, like all organisms, the expressed genome can vary somewhat through mutations. Billions of bacteria when treated with an antibiotic will usually be killed by the drug; however, a few may express a gene which is mutated either spontaneously or by selection, producing a product that essentially escapes the action of the antibiotic. An often used example is of the beta-lactamases, an enzyme that both Gram positive and Gram negative bacteria can express. Beta-lactam antibiotics include penicillin and cephalosporin (see Table 1) which are inactivated by the presence of a beta-lactamase and it includes a large number of antibiotics developed over the years which have been in the market.

An important structural chemical component of these antibiotics is a beta-lactam ring which is disrupted by the beta-lactamase, rendering the antibiotic ineffective. As the antibiotic interferes with the synthesis of the bacteria cell wall making the organism fragile, formation of resistance overcomes the antibiotic and making infectious bacteria multiply rapidly. To overcome the beta-lactamase resistance, some antibiotics, such as augmentin have been developed that included a specific inhibitor of the beta-lactamase. Resistance carries an economic toll increasing health care costs as well as increased suffering and morbidity for affected patients (6). At present, resistance is very common particularly to Gram-positive, MRSA, Enterococcus and more recently to Gram-negative bacteria such as Pseudomonas sp. and these infections account for a large number of hospital and nursing home associated deaths (7-9).

Although resistance to penicillin was initially seen in the 1940s, issues with increasing resistance moved slowly despite an increasing number of scientific publications.
noting various aspects of resistance. As bacteria modified the structure of the proteins to which penicillin binds a new bacteria emerged, the methicillin–resistant Staphylococcus aureus or MRSA which has had a major impact on health care costs and mortality. The basic organism, Staphylococcus aureus, is a common pathogen often living on the skin or in the nose (Figure 3).

Serious infections are often associated with patients with weak immune systems, the sick, elderly, or in long term care facilities. The term methicillin resistant is from the antibiotic, methicillin, a beta-lactam antibiotic that was used for treatment of MRSA, but although replaced now, it is still used to define this type of bacteria. The infection caused by MRSA is not always more serious than other infections, but the problems arises due to the resistance as the bacteria cannot be brought under control, prolonging recovery and tissue destruction. As MRSA was primarily a hospital acquired infection, it was not so widely spread, but now there is a community acquired MRSA, Com-MRSA, which is seen in otherwise healthy people who have not been in the hospital. Com-MRSA is often seen as a serious skin infection which is not easy to treat and can spread to other vital organs. On a practical note, the hand-washing campaigns that are frequently seen throughout Southeast Asia are an attempt to diminish the number of skin associated MRSA infections.

### Antibiotics Fighting Resistance

The broad range of beta-lactam antibiotics which account for a large majority of antibiotics in the market or that have been developed are ineffective against MRSA, these antibiotics include the penicillin and cephalosporin. The penicillin include a chemical family of methicillin, dicloxacillin, nafcillin, oxacillin, as well as other members. Although, methicillin is resistant to beta-lactamase and is able to bind to penicillin-binding proteins and inhibit the synthesis of an important component of the cell wall of the Gram–positive bacteria, peptidoglycan, it is no longer used due to the fact that other antibiotics have fewer side effects and are easier to administer. However, it is important to notice that the critical need to eliminate this infection has prompted the development of specific antibiotics that deal effectively with MRSA and by extension Gram–positive organisms. However, the antibiotics that have been developed for this purpose are generally used specifically for MRSA and some variants such as VRE, vancomycin resistant Enterococcus.

The first of these “last resort” antibiotics was vancomycin, a glycopeptide which was actually discovered in 1953 (Table 1). It originated from soil bacteria and was found to avoid the development of resistance from Gram-positive bacteria making it the choice for treatment of MRSA. This property led to rapid approval in 1958. Although vancomycin had drawbacks, it has poor absorption when taken orally so the usual route of administration is intra-venous, but an oral version was approved in 1986 for use with C. difficile. A second antibiotic in this category is daptomycin, a lipopeptide from natural sources. It is a soil bacteria which was actually discovered in the 1980s but not approved until 2003. It shows efficacy in treating resistant forms of Gram–positive bacteria by disrupting several aspects of bacteria cell membrane function and leads to a loss of membrane potential, as well as inhibition of protein, DNA and RNA synthesis and finally bacteria cell death. A recent entry into the antibiotic spectrum for serious Gram-positive infections, linezolid is somewhat unique as it is a completely synthetic antibiotic. Linezolid was discovered in the 1990s and its approval for clinical use was granted in 2000. The mechanism of action is not completely understood but it seems to inhibit protein synthesis at the stage of initiation. It has a good safety profile as it is not broken down through the cytochrome P450 mitochondrial pathway which is unlike many antibiotics and antifungals in current use. Resistance to vancomycin and daptomycin has been noted for MRSA as well as another Gram–positive bacteria, Enterococcus (10, 11); however, daptomycin may have more robust activity compared to vancomycin and it may actually be a treatment option in the case of vancomycin resistance.

### Developing Antibiotics for the Future

It is important to be aware that bacteria resistance will not go away, bacteria that are now showing resistance will remain and others may still develop as genes can be shared laterally. Even if new types of antibiotics are successfully developed that
do not select resistant bacteria, it would not be possible to eliminate all resistant bacteria.

The question is then how the situation stands now. In the early days of developing antibiotics, it was necessary to show their efficacy. Now, there is an emphasis on showing that resistance develops more slowly or not at all. Vancomycin was an early attempt at that concept which was not successful. A recent review has found that 20 antibiotics were approved since 2000 and about 40 new antibiotics are in the current pipeline (12). Of these new antibiotics, 11 were from natural products and 9 are synthetic. However, the antibiotics from natural sources, largely fungi and mold, are of a class that has already shown resistance and similar issues are expected when their usage increases. From the class of synthetic antibiotics, most are from the quinolone class. Other members of that class show toxicity and resistance.

An unique class of antimicrobials is found in nature which function similar to those derived from fungus. They protect the organism from pathogenic invasion and are referred to as host defense peptides or defensins (13). These have not found clinical application as yet but there are a number of potential advantages such as the ability to modulate the host immune response and some may be anti-inflammatory. Reviewing this area of research shows that it is feasible to use some of the chemical features of naturally occurring antimicrobials to create new molecules that are actually much more active against bacteria than the naturally derived molecules (14).

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Over dinner one day, my General Practitioner friend recalled how his daughter developed wheezing while travelling in Australia, and how he had put her on antibiotics in case she had bronchiolitis and he did not wish to take "chances" in a foreign land. The Australian doctors were quite shocked at the practice, as the cause for bronchiolitis is almost always viral. However, at the same dinner conversation, another doctor friend who is prone to recurrent sinusitis, mentioned that while she knew the cause of sinusitis is mainly viral in aetiology, she has had enough experience that in her case, she often ended up with a secondary bacteria infection, and so she takes antibiotics empirically. She does not send specimen for culture and testing; she knows what works best for her.

So are doctors over treating with antibiotics? Should they send specimens for culture, and treat with antibiotics only when it is confirmed that there is bacterial growth? And if it is bacterial in aetiology, should doctors use susceptibility results to guide them on the choice of the antibiotics?

Being a microbiologist and specifically a bacteriologist, I may have a bias for culture and susceptibility testing. I believe there is value in culture, and indeed there is a time and place for all things, and certainly a time for culture.

Most times, when a patient consults a doctor for the common diseases with infectious aetiology, the problem is more likely viral than bacterial, so there is certainly...
no need to do any microbiological tests or bacterial cultures. There is certainly no need for antibiotic therapy in such cases.

There are however, infections at certain sites which are more likely bacterial, and these are urinary tract infection, keratitis, cutaneous abscesses and other wound infections, as elaborated below. The value in culturing infections from these sites is first of all, we can confirm what is the causative microbial agent, and secondly, if it is a bacterial infection, we know what antibiotics are expected to work. Giving the appropriate antibiotics will enable the patient to make quick recovery, and save the patient from suffering prolonged illness with inappropriate treatment, sometimes with serious consequences.

The following clinical conditions (with focus on community-acquired infections), may be bacterial in aetiology, and hence benefit from laboratory work-up including bacterial culture and susceptibility testing:

1. Urinary tract infection

This is the bugbear of many females, and is invariably bacterial in aetiology, with *Escherichia coli* the most common bacteria. However, there is increasing rate of resistance, and many oral antibiotics are now no longer effective.

2. Wound infections

Wounds are often caused by bacteria. *Staphylococcus aureus* is often the cause of abscesses, and although standard antibiotics are often effective, there is now an increasing incidence of community acquired MRSA, which only bacterial culture with susceptibility testing will reveal. Cellulitis, on the other hand, is largely due to *Streptococcus*, which remains susceptible to usual therapy, and in reality is often difficult to get a sample for bacterial culture, and is thus often treated empirically.

3. Keratitis

Its causes can be bacterial, fungal, viral or parasitic. Bacterial infection is quite common especially if trauma-associated. Common bacteria are *Staphylococcus aureus* and *Pseudomonas aeruginosa*, both of which are generally quite susceptible to the standard antibiotics, but there could be exceptions.

4. Genital infections

They can be sexually transmitted like *Neisseria gonorrhoeae*, which usually needs culture proof.

Non-sexually transmitted infections include *Candida* vaginitis, which is fungal but can be easily cultured using bacteriological methods, and possibly bacteria like anaerobic bacterial vaginosis.

5. Pneumonia

Pneumonia usually affects high risk people like the elderly, the very young, and those with risk factors like immunosuppression, heart and lung disease. Community-acquired bacterial pneumonia can be due to *Streptococcus pneumoniae* (trend of increasing resistance world-wide), *Haemophilus influenzae*, *Branhamella catarrhalis*, or other non-culturable/hard to culture bacteria like *Legionella, Mycoplasma* and *Chlamydia*, which may require other diagnostic modalities like serology or PCR. Other causes of pneumonia can be viral, for instance, Influenza, RSV etc. Hospital acquired pneumonias are caused by a numerous number of bacterial species, and are often multi-resistant, that is, resistant to several groups of antibiotics.

6. Gastroenteritis

Mainly viral, for example *Norovirus* which can cause outbreaks in closed community, or toxin-related (hence, non-culturable). Less commonly are bacterial causes like *Salmonella Enteritidis* and other *Salmonella* species, *Campylobacter* species, *Vibrio* species, *Shigella* species. Some of these bacteria are getting more resistant, although most Salmonella gastroenteritis is generally self-limiting and should not be given antibiotics as this may prolong the carriage state. Laboratory support is also useful to diagnose parasitic causes.

So the pertinent question is, ‘Can we just give a guess and start empirical treatment?’ Much will depend on the experience of the physician. If the physician is quite sure it is bacterial infection, antibiotics may be needed, but he/she will need to hazard guesses, and the antibiotic chosen may not be suitable. If there are no facilities for culture, this may have to be the route to adopt. However, in countries with good laboratory services, the service should be taken up and cultures done as a good clinical practice, and to guide treatment.

With the rising trend of bacterial resistance, it can no longer be assumed that what worked just last year, may still work now. Bacterial resistance has escalated very quickly, and this is a worldwide trend. With mobility of people, resistance strains cross borders with ease, so we are seeing foreign patients with unusual bacterial resistance. And our local population may have picked up a resistant strain overseas, and returned with these resistant strains. It is no longer possible to guess what is happening to patients, and so sending specimens for bacterial culture
and antibiotic susceptibility testing may be necessary.

There are certain things/pitfalls that have to be noted, when doing bacterial cultures. The quality of the specimen is of utmost importance. As the saying goes, “rubbish in, rubbish out”. The patient should not be paying for a test that is not useful, or even inaccurate. The following must be observed:

1. The specimen collected must be in sufficient amount. Too small a quantity may lead to a sampling of an area without the microbe (or insufficient microbe), hence leading to a false negative result – when there was a bacterial infection

2. The specimen must be correctly collected. Incorrect collecting could lead to problems in interpretation and spurious results. A typical example is urine culture from an ambulant person. The person should be taught to clean the perineum area well, then submit a mid-stream urine. Otherwise the perineal flora could be mixed with the urine, get into the urine, and get cultured and reported, when these are not the cause of the urinary infection

3. There must be timely delivery of the specimen to the lab for culture, otherwise the bacteria may become non-viable, or in the case of urine, because urine is a good culture medium the bacterial starts multiplying to a level that is deemed significant, when they may not be actually significant.

4. All patients should be cultured before the start of antibiotic therapy. Even one dose of antibiotics can compromise recovery and growth of the bacteria, even though the antibiotic may be sub-optimal, that is, the bacteria is resistant to the antibiotic. This point is very important, but often overlooked. We see this problem often in our laboratory practice, whereby the patient may be suspected of a bacterial infection, but all cultures are negative. It is likely that the patient could have presented to the General Practitioner and given antibiotics, and now presents to a hospital specialist, who then orders cultures, which unfortunately, may be negative. It is a really good practice, that if bacterial infections are suspected, to send off for cultures before starting antibiotics. Culture results may take a few days to complete, and in the meantime some empirical treatment could be given. Other tests could also be done at the same time if indicated, such as full blood count, to see if the infection is more viral or bacterial; and if the picture is more like viral, antibiotics can be withheld.

Clinical information is very useful, and can be important when requesting for bacterial culture. Such information will help the laboratory perform the testing as best as possible targeted to the type of aetiologic agents suspected. So clinical diagnosis, relevant history including travel, any suspected aetiologic agent, and antibiotic given or to be given will be useful.

There are some fastidious bacteria that require special media – eg directly plating onto media at beside for Neisseria gonorrhoea, the use of transport media for anaerobic bacteria, the maintenance in cold (ice) for Helicobacter pylori, etc. The laboratory staff or Microbiologist can advise the appropriate specimen to collect, and any special procedures required for delivery and transport of the specimen.

In summary, there are benefits of doing bacterial culture and susceptibility testing, especially in some clinical conditions. Much will depend on the experience of the physician whether therapy should be started without doing laboratory tests. But where in doubt, and if laboratory support is available, it is good practice to send off laboratory tests, which could include microbiological tests like bacterial culture and antibiotic susceptibility testing. The microbiologist can also advise what is the best specimen to submit, and how to collect specimens, and also suggest empirical antibiotic therapy based on laboratory trends, if necessary. However, susceptibility testing of bacteria for the individual patient with a bacterial infection is best, rather than rely on epidemiological trends, in view of the rate of increase in antibiotic resistance amongst some bacteria. Patients who have been healthy with no significant past medical history or recent antibiotic use have been infected with multi-resistant bacteria – this is, indeed, a cause for concern and makes antibiotic susceptibility testing worth doing.

About the Author

Dr Tan Ai Ling is Senior Consultant and Head of the Diagnostic Bacteriology section of the Department of Pathology, Singapore General Hospital. She graduated from the National University of Singapore in 1981, and subsequently trained in Microbiology. She obtained the Diploma in Bacteriology (University of Manchester) in 1986 and the Fellow of the Royal College of Pathologists of Australasia in 1989. She was awarded a HMDP Fellowship in Mycology and Laboratory Quality Assurance from October 1993 to January 1994. Her interests are in Mycology and general Bacteriology. She is the chairman of the department’s Laboratory Quality Committee which oversees quality, accreditation and safety issues. She is also a member of the hospital’s Infection Control Committee.

She has been appointed by the Specialist Accreditation Board to chair the Microbiology Subcommittee of the Pathology Specialist Training Committee since August 2004. The committee sets the direction of training of Microbiologists in Singapore.

She received the Minister of Health Award on 10 July 2006 for work done in Fusarium keratitis outbreak. She was the Singapore Society of Pathology Becton Dickinson Award recipient in 2008, an award given to Pathologists in Singapore for contributions to Pathology.
The development of antibiotics was truly one of the greatest advances in medical science whereby previously untreatable and feared infections became readily curable. However, soon after the first antibiotics were developed, antibiotic resistance was detected – mainly in vitro but also in nature. Currently, efficient treatments of many common infections are complicated by the development of drug resistance in causative bacteria.

There are four major means by which the antibacterial agents destroy the bacteria. They are (1) interference with cell wall synthesis, (2) inhibition of protein synthesis, (3) interference with nucleic acid synthesis and (4) inhibition of a critical metabolic pathway. Some bacteria are inherently resistant to one class of antibiotics but usually susceptible to others. The concern is for acquired resistance where once susceptible bacteria develop resistance to widely used antibacterials.

Bacteria often develop resistance to antibacterials by new mutations. This "vertical evolution" may occur in bacteria by different mechanisms such as (1) Altering the target protein to which the antibacterial agents bound to. This may be by either modifying or eliminating that site so that the antibiotics cannot be bound – this occurs with alterations in the penicillin binding protein in the pneumococcus or
Staphylococci. (2) Increasing or producing enzymes that inactivate the antimicrobial agent – most commonly with beta-lactamases which inactivate beta-lactam antibiotics. (3) Altering the bacterial outer membrane, thereby decreasing the entry of the antibacterials into the bacterial cell which can occur with a range of bacteria (4) Efflux pumps in the bacteria which expel the antibiotics, most commonly in Pseudomonas and other gram-negative bacterial species.

Bacteria can also acquire drug resistance by gaining genetic material from other resistant bacteria in the environment or horizontal evolution. This may occur by (1) Conjugation: Transfers of plasmids containing resistant genes directly from another bacterium (2) Transduction: Transfers resistance genes from one bacterium to another by bacteriophages. This method is now considered to be uncommon. (3) Transformation: Bacteria acquire and incorporate the DNA segments that were released by other bacteria into the environment.

Multi-drug resistance is clearly a potential public health threat given the emergence of many of these antibiotic resistant strains worldwide. According to the US Centers for Disease Control and Prevention (CDC), more than 70% of the hospital acquired infections in the US are resistant to at least one class of antibiotics. Industry funded studies – MYSTIC (Meropenem Yearly Susceptibility Test Information Collection) and SENTRY Antimicrobial Surveillance program, are involved in monitoring antibiotic resistance worldwide. Their results indicate that the antibiotic resistance pattern of bacteria has increased globally in most study sites. A laboratory based surveillance program involving six acute care hospitals in Singapore to monitor the drug resistance pattern of six pathogens namely Staphylococcus aureus, Escherichia coli, Enterococcus spp., Klebsiella pneumoniae, Pseudomonas aeruginosa, and Acinetobacter spp. showed that the problem of antibiotic resistance in Singapore is on the increase. Drug resistance spares no continent and is, in fact, becoming a major concern in Asia. Hospitals, and in particular, the intensive care units are proliferation zones for antimicrobial drug resistance. This is due to the increased usage of antibiotics together with the risk of cross infection in severely ill patients. Many risk factors have been identified for the occurrence of drug resistant bacterial infections among these critically ill patients. These include broad spectrum antibiotic usage, presence of invasive devices such as endotracheal tubes, vascular and urinary catheters, prolonged hospital stay, immunosuppression and malnutrition. Failure to adhere to infection control measures by the healthcare staff, contamination of equipment and the environment are also important modes of transmission of these drug resistant organisms. These drug resistant bacteria among these critically ill patients have consistently been shown to increase the length of stay in hospital, thus increasing the financial burden on the patient as well as on society. The increased mortality due to the presence of these drug resistant organisms is controversial as certain studies have shown limited impact of the multi-drug resistant organisms on overall mortality. This may be related to the fact that many of these infections occur in patients who have multiple comorbidities and are already critically ill from other causes. In these patients, infection with multi-drug resistant bacteria might in fact be a marker for increased mortality rather than a cause of the increased mortality per se.

Among the different groups of resistant bacteria, it has been observed that resistant gram negative organisms are increasing and today the majority of infections especially in ICUs in Asia are caused by multi-drug resistant gram negative bacteria. This trend is also being observed all around the world and is a potentially dangerous threat. These organisms are associated with pneumonia, blood stream infections, urinary infections and surgical site infections. Data from the US National Healthcare Safety Network (NHSN) has shown that 30% of overall hospital acquired infections are due to gram negative bacilli largely associated with pneumonia and urinary tract infections. The annual report of the European Antimicrobial Resistance Surveillance (EARS) network has stated that the resistant Escherichia coli, Klebsiella pneumoniae and Pseudomonas aeruginosa have been steadily showing an increase. Studies from Singapore have also shown that there is diminishing susceptibility to antibiotics among the gram negative bacteria. The important
gram negative bacteria in health care settings that are difficult to treat because of resistance are Acinetobacter baumannii, Pseudomonas aeruginosa, ESBL producing Klebsiella pneumoniae and Escherichia coli. Antibiotic susceptibility patterns in the ICU of a hospital in Indonesia showed the predominant pathogens were Pseudomonas aeruginosa (26.5%) followed by Klebsiella pneumoniae (15.3%)15. In Thailand, among device associated infection from the medical and surgical ICUs showed that among the resistant gram negative organisms, Acinetobacter baumannii was the commonest followed by Klebsiella pneumoniae, Pseudomonas aeruginosa and Escherichia coli16. The International Nosocomial Infection Control Consortium findings pertaining to device associated infections in ICU of seven Indian cities showed that 27.5% of hospital acquired infections were caused by multi-drug resistant Pseudomonas spp followed by multi-drug resistant Acinetobacter baumannii17. Many studies from other parts of Asia have also shown that these drug resistant Acinetobacter baumannii, Pseudomonas aeruginosa, Klebsiella pneumoniae and Escherichia coli were the organisms that were most frequently isolated from the cultures of the critically ill patients18,19,20,21. The Study for Monitoring Antimicrobial Resistance Trends (SMART) investigating the antimicrobial profile of intra-abdominal infections due to Gram negative bacilli in Asia has showed that there are a few of Extended-spectrum beta-lactamase (ESBL) producing K. pneumoniae that were resistant to carbapenems especially from the isolates from ICU signaling the emergence of extremely difficult to treat infections22. More recently, the emergence of NDM-1 and KPC beta-lactamases23,24,25 has raised the specter that these resistant gram-negative infections can even become untreatable or pan-drug resistant with only recourse to much older and more toxic antibiotics such as the polymyxins including colistin. Studies have been carried out on these critically ill patients to determine the major risk factors predicting the occurrence of these resistant gram negative rods (RGNR) in the Asian context. In general, risk factors identified in Asian hospitals tend to be similar to those found in the west26,27,28,29.

ICU admissions, higher severity of illness, increasing age, and surgery have been documented as independent risk factors by many studies30,31,32,33,34. The presence of invasive devices such as the endotracheal tubes, central venous catheters and urinary catheters are also important factors for the acquisition of the RGNR infection35,36. Almost all of the studies have pointed out that previous use of broad spectrum antibiotics carries a higher risk of resistance among the gram negative bacilli17,27,28. These studies suggest that empirical antibiotics should be used judiciously so as to reduce occurrence of multi-drug resistant gram negative organisms.

The impact of these RGNR can be evaluated from both clinical and financial aspects. From a clinical point of view, the outcomes that are most important are the attributable mortality and the length of stay at the hospital or the ICU. The clinical outcome of mortality that is attributed to the multi-drug resistant gram negative organisms’ remains controversial. Certain studies have showed that the resistance of the gram-negative bacilli such as Escherichia coli, Acinetobacter spp are a cause for increased mortality39,40 whereas it has been highlighted by others that the resistant gram negative bacterial infections are not associated with increased hospital mortality41,42. Patients with RGNR infections have been found to have longer hospital stays or ICU stays, although their overall mortality outcome was similar to those without resistant bacterial infections43,44. It is felt by many that initial appropriate antibiotic therapy is the reason for better outcomes amongst these groups of Resistant Gram-Negative Rods (RGNR) patients rather than the effects of drug resistance per se. On the other hand, it has also been shown that even short durations of broad spectrum antibiotics can lead to the development of antimicrobial resistance45, thus calling into question a strategy of de-escalation from empiric broad spectrum initial antibiotic therapy.

As these RGNR infections increase the hospital stay for a patient, they usually result in an increase in the total costs for the patient and loss of bed days to the hospital. A retrospective matched cohort study from Taiwan showed that patients with multi-drug resistant Acinetobacter bacteremia experienced two times more hospital costs as compared with the controls. In addition, they also showed that the costs for antibiotic therapy were higher among the cases46.

There are mixed reviews of utilizing routine surveillance cultures which detect asymptomatic carriers to select empirical antibiotics and control cross infection in ICU patients. A study by Hayon et al47 obtained surveillance cultures to effectively treat even before the onset of Ventilator Associated Pneumonia (VAP) found that only 33% of surveillance cultures matched the actual organisms causing VAP which required microbiologic processing of protected specimen brush (PSB) or bronchoalveolar lavage (BAL) samples. In another study by Bouza et al48, similar results were obtained where only one third of the patients with a VAP had the same microorganism causing pneumonia as the surveillance culture. Routine and strict surveillance may be necessary to identify the high risk patients colonized with resistant organisms who might then go on to develop clinical infections or act as sources for cross transmission. On the other hand, routine surveillance if not properly handled can lead to inappropriate treatment. Organisms which are simply colonizers may end up getting treated and this paradoxically increases the risk of even more resistance being selected out.

Invasive devices are a major risk factor for resistant gram negative bacterial infections; steps should be put in place to either reduce the use of these devices or to use novel coated devices or other technological solutions. Studies have shown that impregnated devices reduce adherence of bacteria to the devices potentially reducing the incidence of RGNR infections49,50. Unfortunately, clinical trials have failed to show consistent improvements in infection rates or mortality although there have been some promising results – in particular with silver coated endotracheal tubes51 or with coated central venous catheters52,53. One problem with these devices is the need to maintain antibacterial activity over time while not releasing potentially toxic products into the host.

New antibacterial agents are not being introduced in pace with the growth of
multi drug resistant organisms. Many novel antibiotics are targeted at gram-positive organisms which are more common in Europe and North America. There are no new agents in the pipeline for resistant gram-negatives as the current reimbursement structure for medications does not encourage innovation in antibiotics. Antibiotics are used for short term critically ill patients as compared to drugs for hypertension or hyperlipidemia or even HIV which are used lifelong.

The Infectious Diseases Society of America’s (IDSA) antimicrobial availability task force has identified six pathogens, the so-called ESKAPE organisms (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter species) as problematic organisms and is encouraging new antimicrobial research to combat them. IDSA has called for combined efforts from industry, academia, the National Institutes of Health, the Food and Drug Administration, the Centers for Disease Control and Prevention, the US Department of Defense, and the new Biomedical Advanced Research and Development Authority at the Department of Health and Human Services to combat this issue.

Antimicrobial resistance is a major worldwide problem. Untreatable infections threaten the gains of healthcare in the last century. Advances in chemotherapy as well as the use of new monoclonal therapies have improved outcomes in many areas of healthcare but many of these are accompanied by increased risk of infection. In the recent past, these infections were easily treated but the same unfortunately cannot be said today. A concerted effort by industry and academia is needed to find solutions to this pressing problem.

References


About the Authors

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Antibiotics and Resistance in Ocular Infections—Indian Perspective

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Abstract
As in many parts of the world, infections of the eye are common in India and a wide variety of antibacterial as well as antifungal antibiotics are available in the market. Antibiotics can be administered in the eye by a number of routes; topical, subconjunctival, subtenon and intraocular. Peculiar to the treatment of eye infections, fortified eye drops from parenteral formulations are often used. These preparations achieve high concentrations; usually much above the minimum inhibitory concentration (MIC). Fair amount of research on antibiotic resistance in India deals with bacterial infections, however, studies on antibiotic susceptibility of fungal isolates are limited. The resistance in bacteria seems to be increasing in parallel with the increase seen over the years in bacteria associated with systemic infections. Although it is believed that the rise in resistant ocular bacterial isolates is linked to the rise in resistant systemic pathogens, recent evidence has correlated the emergence of resistant bacteria in the eye to prior topical antibiotic therapy. Probably, either of these contributes to the emergence of resistance among bacteria and fungi associated with eye infections. This review describes the current scenario of antifungal and antibacterial susceptibility of fungi and bacteria associated with eye infections with special reference to the Indian subcontinent.

Introduction
Micro-organisms are closely associated with the eye forming the microbial flora of the external ocular surface at birth while the inner parts of the eye remain sterile. Several mechanisms in the extraocular surface protect the eye and only a breach in surface epithelium due to trauma or lowering of local or systemic immunity may predispose the eye to infections. Several mechanisms in the extraocular surface protect the eye and only a breach in surface epithelium due to trauma or lowering of local or systemic immunity may predispose the eye to infections. In addition, the number and virulence of the invading organisms play an important role in launching an infection. The resident bacteria of the conjunctival sac or the environmental bacteria or fungi can establish infection and need to be treated with antibiotics. Occasionally, endogenous infections arising from other parts of the body may affect the eye. Ophthalmologists have at their disposal a large repertoire of antibacterial and antifungal antibiotics (eye drops, ointments, tablets and parenteral). These are in use since the beginning of the antibiotic era and similar to other infections. Antibiotic resistance in eye infections is a matter of concern to the ophthalmologists and microbiologists. Until recently it was thought that the source of resistant bacteria or fungi in eye infections is an outcome of the organisms acquiring resistance during treatment of systemic diseases. Although not yet demonstrated for fungi, evidence in literature suggests emergence of resistant bacteria in the eye owing to prior antibiotic therapy of the eye.[1] This review presents the Indian perspective of antibiotic resistance among bacteria and fungi causing eye infections.
Barriers to entry of drugs into the eye

In a normal eye, transfer of antibiotics from ocular surface to the inside of the eye and from blood to ocular tissues is hindered at various levels (Figure 1). The surface epithelia of the bulbar conjunctiva and the cornea are relatively impermeable, especially to water soluble agents.

A breach in surface epithelium allows the entry of these drugs more effectively in the anterior segment of the eye. However, because of the diffusion barrier across the lens zonule compartment and anterior vitreous, entry of drugs through cornea and conjunctiva does not reach the posterior segment of the eye. Inability of the drugs to reach the posterior segment from the anterior segment is also due to movement of the aqueous from the posterior chamber through the pupil and its drainage into the venous circulation. Barriers of the surface epithelium may be overcome by subconjunctival and subtenon injections. While a blood-aqueous barrier inhibits the entry of water soluble drugs across the ciliary body epithelium, the blood-retinal barrier limits the entry of drugs into the retina. Diffusion across the outer retina is blocked by cells of retinal pigment epithelium which constitute the outer blood-retinal barrier. Resistance across the retinal capillaries by endothelial tight junctions is known as inner blood-retinal barrier. These barriers are partially broken down in presence of inflammation. Understandably, direct intraocular injections always achieve higher concentration compared to systemic administration of drugs.

Antibacterial and antifungal drugs used for the treatment of eye infections

Unlike many other organs in the body the eyes are amenable to antibiotic therapy by a number of routes such as topical, subconjunctival, subtenon, intraocular etc. Several commercial eye drops are available in the required concentration. However, eye is probably the only structure for which fortified drops at higher concentrations are used that may achieve bio-availability of the drugs higher than minimum inhibitory concentrations (MIC) for the offending organisms. Antifungal as well as antibacterial fortified topical drops are generally prepared aseptically from parenteral drugs. Using distilled water as solvent to make fortified drops runs the risk of contamination. Therefore, they are preferably dissolved and diluted in artificial tear preparations to avoid contamination. Table 1 lists the antibacterial drugs that are currently in use, and their mode of action. [2]

The major groups of antifungal drugs are azoles (ketoconazole, fluconazole, itraconazole, voriconazole, imidazole, miconazole) and polyenes (amphotericin B, natamycin, nystatin) that are respectively fungistatic with interference in protein synthesis and fungicidal with action on cell wall function. Antifungal activity of cationic antiseptics such as chlorhexidine and polyhexamethylene biguanide, which are amoebicidal and function by creating pores in the cell membrane, is also well known.

For most eye infections the therapy is topical instillation of antimicrobial eye drops. In bacterial and fungal keratitis the patient is given a topical commercially available eye drop or fortified eye drop, with or without systemic treatment. Frequency of instillation varies from disease to disease. In contrast, intravitreal therapy is preferred for many intraocular infections with or without systemic therapy. Subconjunctival and subtenon injections may be preferred under special circumstances.
Development of Drug Resistance among Ocular Pathogens

Resistance among ocular pathogens seems to be increasing in consonance with the increase of resistance among bacteria and fungi associated with systemic infections. The factors contributing to development of drug resistance among ocular bacterial isolates include overuse of antibiotics for systemic infection as well as overuse of topical antibiotics in the eye. [1] Other factors that may contribute are improper dosing regimen, misuse of antibiotics for viral infections, extended duration of therapy and not to a small extent current globalization and migration of populations.

Topical antibiotics that are in common usage for the treatment of bacterial conjunctivitis include aminoglycosides, polymyxin B combinations, macrolides and fluoroquinolones. Although not used in the United States for its side effects, chloramphenicol is commonly used in India. Streptococcus pneumoniae is a common cause of conjunctivitis and usually a sensitive organism to a large repertoire of antibiotics. However, resistance to gentamicin was reported 42.3% in 1997 which increased to 56% in the year 2000.[4] Similarly, resistance to tobramycin rose from 43.6% in 1997 to 46% in 2000. Azithromycin is a recently recommended broad spectrum drug for the treatment of bacterial conjunctivitis, however, moderate to very high resistance to azithromycin has been reported for H. influenzae, S. pneumoniae, S. aureus and S. epidermidis isolates from bacterial conjunctivitis. Fortunately, Haemophilus influenzae, a common cause of bacterial conjunctivitis, remains sensitive to aminoglycosides and polymyxin B.

Methicillin resistant S. aureus (MRSA) has emerged as a dreaded organism for its wide range of resistance to several groups of antibiotics. Its prevalence in conjunctivitis is highly variable. One study has shown an increase in MRSA in bacterial conjunctivitis from 4.4% (1994-5) to 42.9% (2002-3).[5] Situation in coagulase negative staphylococci (CoNS), a common cause of keratitis and endophthalmitis, is no less precarious. Until 2003 approximately 19% of CoNS were reported to be resistant to gentamicin and 2% were resistant to gatifloxacin. [6,7] However, by the year 2006, nearly 11% of CoNS from normal ocular surface and 53% of CoNS from endophthalmitis were reported to be resistant to gatifloxacin. [8] All ciprofloxacin resistant MRSA and methicillin resistant S. epidermidis (MRSE) demonstrate resistance to 4th generation fluoroquinolones such as gatifloxacin and moxifloxacin but not to besifloxacin, the latest among the fluoroquinolones. [9] Currently not available in India, besifloxacin is the first fluoroquinolone that has been developed only for ophthalmic use. In vitro activity of besifloxacin shows lower minimum inhibitory concentration (MIC) compared to all other fluoroquinolones and azithromycin. [10] Reduced susceptibility of S. aureus to vancomycin was first noted in Japan in 1997 in systemic infections.[11] Using disc diffusion susceptibility testing method there are some reports of vancomycin resistant S. aureus (VRSA) ocular infections [12-14] however, till date there are no confirmed VRSA ocular isolates.

Pseudomonas comes next to staphylococci in its importance as a causative agent of eye infections. It tops the list of challenging organisms to treat because of high prevalence of resistant strains. Most strains of P. aeruginosa isolated from contact lens associated corneal ulcers were resistant to ampicillin, cephalothin, neomycin and tetracyclins.[15] In the last decade topical ciprofloxacin replaced aminoglycosides and became the best drug to treat P. aeruginosa keratitis. It probably resulted in over use as the preferred antibiotic for preoperative prophylaxis in eye surgeries. Multidrug resistant P. aeruginosa have been reported from keratitis and endophthalmitis patients leaving no choice but to use piperacillin/tazobactum or imipenem for the treatment of such cases.[16,17] The landmark multicentric study from the United States - Endophthalmitis Vitrectomy Study-reported 11% of gram negative organisms

<table>
<thead>
<tr>
<th>CLASS OF DRUG</th>
<th>TYPE OF DRUG</th>
<th>MODE OF ACTION</th>
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</thead>
<tbody>
<tr>
<td>Penicillins/cephalosporins</td>
<td>Bactericidal</td>
<td>Cell wall inhibitor</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Bactericidal</td>
<td>DNA gyrase inhibitor</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Bacteriostatic</td>
<td>Inhibitor of protein synthesis</td>
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<tr>
<td>Erythromycin/azithromycin</td>
<td>Bacteriostatic/Bactericidal</td>
<td>Inhibitor of protein synthesis</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Bacteriostatic</td>
<td>Inhibitor of protein synthesis</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Bactericidal</td>
<td>Inhibitor of protein synthesis</td>
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Table 1: Common antibacterial drugs used to treat eye infections and their mode of action
to be resistant to amikacin and ceftazidime. [18] In contrast, the level of resistance in gram negative organisms associated with endophthalmitis was higher in a study from India at 39% to ceftazidime, 18% to amikacin and 13% to ciprofloxacin. [19] The same group has recently reported with serious concern a high level of multidrug resistance (MDR) among gram negative bacteria causing endophthalmitis in Indian patients. [20] This study also reported MDR enteric bacteria such as Escherichia coli and Klebsiella pneumoniae from patients with endophthalmitis with poor visual outcome. Among Enterobacteriaceae isolated from eye infections in another study, the resistance to gatifloxacin was 3.4%, to ofloxacin and ciprofloxacin was 5.1% and to gentamicin was 8.5%. [21]

Information about use of linezolid to treat ocular infections is limited. In a patient with vancomycin resistant Enterococcus faecium endophthalmitis, intravenous and oral linezolid led to resolution of infection.[22] Reports of vancomycin resistant Enterococcus (VRE) ocular infections are rare. In a series of 26 cases of E. faecalis endophthalmitis, between 1995-2007 from India, there was one VRE. [23]

The drug of choice for the treatment of infections caused by non-tuberculous mycobacteria and Nocardia species is generally amikacin and all ocular isolates are reported to be susceptible to this drug.[24,25] Closely classified with these organisms are non-diphtherial Corynebactrium species which have recently been recognized as ocular pathogens. C. macginleyi is said to be associated with conjunctivitis and keratitis and reported to be sensitive to a large number of antibiotics including fluoroquinolones. However, what may be an alarming signal, 11 out of 16 C. macginleyi isolates from normal conjunctiva were found to be resistant to three fluoroquinolones (ciprofloxacin, norfloxacin, levofloxacin) by E test.[26]

Susceptibility test results for fungal isolates from the eye against antifungal antibiotics are limited. A recent study from L V Prasad Eye Institute in India, tested 60 isolates from fungal keratitis against natamycin and found low MIC of natamycin (<16 μg/ml) for all isolates except Aspergillus flavus. [27] Sometime back, another study from India reported the susceptibility of fungal keratitis isolates to ketoconazole and fluconazole. While two thirds of the isolates were resistant to fluconazole, variable sensitivity ranging from MIC of 0.5–10 mg/ml was found among others. Most of the isolates were Aspergillus species. [28] The authors however, did not comment on the breakpoint they considered for determining the susceptibility level of the isolates. An interesting study from Aravind Eye Hospital in India showed antifungal activity of antibacterial antibiotics such as tobramycin, moxifloxacin and chloramphenicol against Fusarium and Aspergillus species isolated from fungal keratitis patients. [29] This may explain the anecdotal reports of fungal keratitis responding to inadvertent treatment with antibacterial antibiotics. However, the MIC90 of these drugs was much higher (500-1000μg/ml) than what is achieved with antifungal agents and surely they are not recommended for the treatment of fungal keratitis. The same study showed a low MIC90 (16–32 μg/ml) of benzylkonium chloride against these fungal isolates. Benzylkonium chloride is a common preservative used in commercial eye drops and this may further explain the occasional response to antibacterial antibiotics. Over 90% isolates of Fusarium and Aspergillus were found to be sensitive to natamycin and itraconazole respectively in a study on large number of fungal keratitis isolates from China. [30] Currently, natamycin remains the drug of choice for fungal keratitis caused by filamentous fungi.

Testing of bacterial and fungal isolates for susceptibility to Drugs

Emergence of antifungal drug resistance has made it important to test for susceptibility although the in vitro results may not correlate with the treatment outcome. Techniques for performing antifungal susceptibility testing have usually been difficult which has led to dearth of studies on antifungal susceptibility, especially in ocular microbiology. Antibiotic concentration in ocular tissues during topical therapy is difficult to measure, therefore, ocular tissue-specific breakpoints are not yet available to use for determining the susceptibility of ocular fungal or bacterial isolates to antibiotics. Clinical and Laboratory Standards Institute (CLSI) guidelines based on breakpoints derived from serum/plasma/ cerebrospinal fluid levels of antibiotics are used for determining susceptibility of bacterial and fungal isolates from the eye. These systemic breakpoints, however, may have limited predictive value for ocular isolates. Studies are needed to resolve the dynamics of breakpoint versus antibiotic resistance of ocular isolates and their relationship to clinical response. Nevertheless, in absence of a better alternative, the current systemic therapy based breakpoints to determine susceptibility of ocular isolates remains useful. User friendly, well standardized procedure yields consistent results and helps to track trends of susceptibility and compare data. [6] Parmar et al found comparable results between keratitis cure rates and in vitro susceptibility results by disc diffusion method in patients treated with topical gatifloxacin and ciprofloxacin, thus justifying the use of CLSI standards for testing ocular isolates. [31] A good correlation between results obtained with MIC and disc diffusion tests vis-à-vis clinical outcome has been shown in Pseudomonas isolates against ciprofloxacin. [32]

A notable publication by Prajna et al has convincingly shown that eye drop preparations are an alternative to pharmaceutical grade natamycin (not available to most laboratories) for testing antifungal susceptibility.[33] Susceptibility breakpoints for natamycin have not been described so far in CLSI guidelines, however, MIC of 16 μg/ml or less is considered to indicate susceptibility of a fungal isolate.[33]

In conclusion, the treatment of ocular infections is challenging in the face of antibiotic resistance among ocular pathogens. Resistance to most groups of antibiotics is increasing throughout the world including India. There are not many newer antibiotics on the horizon except for few antibacterials such as besifloxacin and antifungals such as voriconazole and posaconazole. Judicious use of antibiotics along with development of new products is the only way forward.
References


About the Author

Dr. Savitri Sharma is the Director of Laboratory Services of L.V. Prasad Eye Institute (LVPEI) network at Hyderabad, Bhubaneswar, Vishakhapatnam and Vijayawada in India. An alumnus of JIPMER, Pondicherry (MD-1982) her field of microbiology focused on the eye when she joined Aravind Eye Care System, Madurai in 1986 where she diagnosed the first case of Acanthamoeba keratitis in India. She moved to the LV. Prasad Eye Institute, Hyderabad in 1991, and reported the first case of ocular microsporidiosis in India in 2003. She is the recipient of several grants and awards from DBT, CSIR, DST, Bausch & Lomb International Research Program, British Contact Lens Association, American Academy of Ophthalmology, All India Ophthalmological Society, Indian Association of Medical Microbiologists etc. Several randomized clinical trials involving contact lenses and treatment of bacterial and fungal keratitis have been monitored by her. She was involved in the development of the Vision Chip (Xcyton) under CSIR (NMITLI) grant. She has been the Editor-in-chief of Indian Journal of Medical Microbiology (IJMM) for eight years and the President of Indian Association of Medical Microbiologists (IAMM) from 2008-9. She has authored a book on "Ocular Microbiology" and has published 12 book chapters and 176 papers (National- 63, International-113) in peer reviewed journals. Her research interests are ocular microsporidiosis, molecular diagnosis, virulence factors, antibiotic susceptibility and pathogenesis of Staphylococcus, Fusarium, Aspergillus, Candida, Pseudomonas associated with eye infections.
Computers, the Internet and mobile communication devices now permeate every aspect of our lives. In 2011, there were nearly 2.1 billion Internet users (or approximately 30.2% of the world’s population) around the globe. In Singapore, 78% of the population are Internet users, a doubling of the 37% just 10 years ago. Nearly 80% of the world’s population own a mobile phone and a quarter of these are smart phone users. Different industries have embraced the marriage between technology and the platform it offers to improve accessibility, propagate information rapidly and streamline processes. Technology has changed the way we buy things, make transactions at the bank and travel. Its impact on traditional areas of education and healthcare is less even. Teachers still largely teach in classrooms and physicians continue to provide medical care in clinics and hospitals. But this is changing.

Technology in Mental Health

The mental health industry is traditionally specialist knowledge driven, labour-intensive and focused on person-centred therapeutic alliance. There is little in terms of using technology in patient care. The argument that because it is a relational science that requires individualised care, technology will only serve to hinder its practice and take away the holistic element of illness recovery centred around the person. In essence, it dehumanises the clinical relationship through the cold application of a standardised process via technology. Yet, there is evidence for the application of technology in mental healthcare. Screening instruments such as structured diagnostic interviews are increasingly computerised. Many other clinical scales are made available for purchase and/or download online. There are websites established by reputable agencies offering materials about mental health issues as well as an abundant number of individuals on the World Wide Web offering therapeutic help. Numerous publications are dedicated to chronicling technological advances in psychiatry and psychology such as the...
Journal of CyberTherapy and Rehabilitation and Cyberpsychology and Behavior. Other traditional scientific journals have started to include special issues on specific, innovative, technology-based treatment modality (e.g. "Cognitive and Behavioral Practice", volume 6). Extensive literature has also been published on the efficacy of the various software and computer systems developed specifically to provide intervention for diverse diagnostic groups. The immersion of technology in mental health has come a long way since the early days when Joseph Weizenbaum wrote the Eliza programme in the 1960s to mimic the human interaction of what a therapist could offer. Eliza responds and replies to typewritten inputs on the keyboard. Technology is more sophisticated now and allows audio and visual inputs to be considered. Take the Xbox Kinect or the Apple Siri systems as examples. This progress has made it possible for clinicians to adapt novel ways of including technology in treatment.

Telespsychiatry

One of the most common examples of the use of technology in mental health would be telespsychiatry. Using video-conferencing technology, it offers remote access to assessment and interventions. An example of this was developed by the Division of Child Psychiatry, University of Toronto more than 10 years ago allowing any child mental health agencies within the pre-identified remotes sites to have access to education, consultation and support via tele-conferencing technology from more than 70 faculty members. The programme provided mental healthcare accessibility to the rural communities which might otherwise be disadvantaged by geographical isolation.

Therapy Transformation

Cognitive behavioural approaches which are a mainstay for psychological interventions in emotional disorders have been translated into computer programmes. Many programmes have been written onto handheld computers that give specific prompts to remind individuals on their treatment goals, therapy homework and self-evaluation. Today, computer-simulated virtual environments are more sophisticated since its earliest inception as a cumbersome head-mounted device in 1968. This allowed clinicians to capitalize its usage as an important technological tool for exposure therapy in anxiety intervention. Exposure exercises that might otherwise be difficult and/or not possible within the constraints of the consult room are now possible with the adaptation of virtual reality. For example, several case studies attested that a computer-simulated airplane environment was effective in treating the fear of flying. Varying degrees of exposures (e.g. takeoffs and landings) can be incorporated in the virtual reality for a tailored treatment plan.

Technology Enhancement

Technology can also be adapted for use as an appendage to standard intervention processes. Preset wrist watches designated to sound at a specific time were given to a group of individuals with binge-eating behaviours. When the wrist watch goes off, the individuals would be required to record down their emotions, distress they might be experiencing, hunger level, food cravings as well as the intensity of their urge for binge eating. Awareness of the severity of their own conditions, coupled with the availability of continuous information recorded will give therapists invaluable materials to work with.

The Drinker's Check-Up is a software programme catering to problem drinkers ambivalent about changing their behaviours. Incorporated with the programme is a comprehensive battery of assessment as well as different treatment strategies sensitive to the motivation to change of the user. It can be administered as a treatment protocol by individuals without formal training in substance abuse and hence, offering a certain level of flexibility in the manpower resource management.

Youths and Technology

Youths have a natural affinity for embracing the use of technology in their lives. Mental health professionals are exploring creative ways of incorporating novel technical elements into clinical work with this population. New generation game consoles such as the Nintendo Wii and the Kinect for Microsoft Xbox360 have been introduced to therapeutic work for a range of therapeutic outcomes. Consequently, clinicians have experimented by using game consoles in various child and adolescent mental health population including children with Attention Deficit Hyperactivity Disorder (ADHD), behavioural difficulties and Asperger's syndrome. Other professionals have developed their own web-based games to target specific areas for change; for example the Reach Out Central web portal (www.reachoutcentral.com.au ) aims to teach adolescents adaptive coping strategies, tolerate psychological distress and cultivate resilience.

At Singapore’s Institute of Mental Health, child psychiatrists and their teams have started examining the effectiveness of technology in treating childhood disorders. Using brain-computer interface (BCI; a direct communication pathway between a human brain and an external device), a series of non-invasive interactive training games were developed to alleviate the inattentive symptoms associated with ADHD; henceforth improving a child's ability to concentrate. A collaborative study is also underway with the Nanyang Technological University on developing behaviour-based interaction architecture (BIA) for a humanoid robot as a vehicle for therapeutic intervention among children with autism spectrum disorder (ASD). It is postulated that a robot is a more predictable medium and can alleviate a certain level of anxiety and stress related to human interactions for a child with ASD. The usage of robotic technology in intervention provides a platform for the child to breakdown learning into smaller more palatable components without being overwhelming.
Vision for the Future

We believe that the vision for mental healthcare like most of healthcare will be a population based one. This population based strategy is necessary because of dual challenge of increasing demands and limited manpower resources. Such a strategy will address the treatment gaps we find in many chronic conditions which are often identified late. Late discovery of illness results in heavy burden for society and the need to build more hospitals and other acute care facilities. Early identification of illness and prevention in high risk individuals require a system that is self-driven yet personalised. As it is impossible to have a large number of clinicians and healthcare providers, such systems would require technology and its applications for every person to be their own specialist. The problem with evidence based treatments is that it is well applied only in excellent medical facilities and will benefit only a portion of society. In the US, this means those who can afford it. In jurisdictions that practice socialised medicine like the UK, it can lead to long waiting times for treatment and usually is for the most severely ill. Technology has the possibility of changing this by identifying problems early or even in implementing preventative strategies within the comfort of ones home, school or workplace. Some of these strategies are already being implemented leveraging on technology and innovation.

Singapore rolled out the National Mental Health Blueprint in 2007. The focus of the Blueprint for children and adolescents is in the school system, as primary school education is mandatory and schools form the most appropriate avenue for preventative and intervention efforts. This led to a partnership between the Ministry of Health, the Ministry of Education and the Ministry of Community Development and Sports to form a community mental health pilot program called “Response, Early Intervention and Assessment in Community Mental Health for Students” (REACH). The primary aims of the REACH program are to train and support school counsellors in the early identification and management of children with behavioural and emotional difficulties. The REACH program comprises a multidisciplinary team of psychiatric residents, psychologists, medical social workers, nurses and occupational therapists. The REACH team works closely with each school to identify children at risk for behavioural and emotional disturbance, including violence, and engages these children and their families into services before the emerging problems become severe. A network of family doctors and social service agencies within the school’s vicinity are also engaged to provide support for these children and their families. The REACH program helps to reduce the stigma associated with seeking mental health services. REACH adopted a variety of tools and resources that were originally designed for use in tertiary child psychiatric settings and then modifies (if necessary) these tools for use in the community, leveraging on technology. A web portal (www.roc-n-ash.com) was used as the entry point for parent and teacher education as well as providing novel web based interventions for anxiety and ADHD. Prototype research on serious games focused on mental health issues such as anger management are being developed as add-ons through the portal including access for counsellors to share materials.

The development of the REACH program is an evolving one that will continue to require an open mind with a passionate heart. The paradigm shift from acute tertiary care in hospitals and clinics to personalised self and family based interventions is not an easy one to accept. Evidence based medicine must move forward for an evidence based delivery system to get the best care to the majority of the population.
Dr Daniel Fung is the Chairman Medical Board at the Institute of Mental Health, Singapore since Dec 2011. He was formerly the Chief at the Department of Child and Adolescent Psychiatry from 2006 to 2011. He is an Adjunct Associate Professor with both the Yong Loo Lin Medical School and Duke-NUS Graduate Medical School, National University of Singapore and the Division of Psychology, School of Humanities and Social Sciences, Nanyang Technological University. He has received several awards including the NHG Distinguished Achievement Award in 2010, PS21 Star Service Award in 2009, National Council for Social Services long service award 2008, the Singapore Children's Society Silver Service Award 2007.

Dr Fung is the Secretary General of the International Association for Child and Adolescent Psychiatry and Allied Professions and the Immediate Past President of the Asian Society of Child and Adolescent Psychiatry and Allied Professions. He is also the President of the Singapore Association for Mental Health, an NGO that supports mentally ill persons and their families in the community.

Dr Fung is a Principal Investigator and Co-Investigator for various studies involving innovative clinical interventions on disruptive behaviour disorders and anxiety disorders. He is also the Vice chairman of the Clinical Research Committee of the Institute of Mental Health. Dr Fung conducts clinical research on disruptive behaviour disorders (E.g. Attention Deficit Hyperactivity Disorder) and emotional disorders (E.g. Anxiety disorders). His recent work involves a randomized controlled trial of fatty acids supplementation and social skills training for children and adolescents with disruptive behaviour disorders. His current interests include new media interventions for psychiatric disorders in children and adolescents. Dr Fung has been involved in over 10 research grants and is a PI in several NMRC funded grants. He has coauthored over 40 research papers, more than 10 books and five book chapters.

Dr Fung is also the programme director of REACH (Response, Early interventions and Assessment in Community mental Health), a community based mental health programme which is part of the National Mental Health Blueprint.

Ms. Nikki Lim-Ashworth has been a Research Psychologist at the Child Guidance Clinic within the Institute of Mental Health, Singapore since 2008. She is currently involved in several clinical research projects on disruptive behaviour disorders. She also provides cognitive behavioural therapy to children with mood and anxiety concerns.

She started her career in as a counsellor in 2004 where she provided therapy for families, conducted behavioural modification workshops for children and was also responsible for managing a major joint HomeCare project with a Children's Hospital in Singapore. She has since worked as a research assistant for the Ministry of Education in Singapore, the Department of Paediatrics at a Singapore hospital before joining the Institute of Mental Health.

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Future Perspectives for Influenza Prevention – A Global Paradox

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Introduction

According to WHO, vaccines are the cornerstone for the control of influenza. Therefore, this global health organization, and many national health authorities, recommend annual immunizations against influenza. The WHO runs a global surveillance system to monitor the continuously changing influenza viruses to identify and recommend each year the best possible vaccine composition for both the Northern- and the Southern Hemisphere.

Influenza surveillance, epidemiological and vaccine research is, relatively, quite new in Asia, and, as a consequence, much of our knowledge of the epidemiology of influenza disease and the vaccines used to protect against it is derived from research carried out in the western world.

In more recent years, particularly since the emergence of the highly pathogenic H5N1 avian influenza virus in the late 1990s, interest in influenza and influenza control has been aroused in developing countries in South East Asia.

For many years, developed countries in the western world have recommended the use of influenza vaccines for certain groups, who were believed to be at increased risk of complications associated with influenza infections. Over time, these countries developed different strategies to advocate vaccine usage and implement vaccination guidelines.

Although influenza immunization implementation strategies need to fit the country-specific circumstances, the collective experience gained during the last 60 years of usage may offer guidance for other countries which may decide to initiate active influenza prevention policy.

In this article, we discuss seasonal influenza disease and control measures as recommended by WHO and many national health authorities. The article provides data to demonstrate the current discrepancy between the target rates for seasonal immunization of elderly and at-risk patients and the actual influenza vaccine distribution rates. This “influenza paradox” is discussed in the context of 1) global efforts to improve vaccine uptake rates, 2) global and regional health initiatives, such as the global action plan for non communicable diseases and healthy ageing and 3) global pandemic influenza preparedness.
Seasonal Influenza prevention in the past

The global annual disease burden associated with influenza infections is well documented in the literature. Local annual epidemics may be as variable and unpredictable as the influenza viruses causing them. In some years, epidemics can have a serious impact whereas in other years the impact may be much less. WHO estimates that, on average, 3–5 million cases occur on an annual basis and 250,000–500,000 people, mostly elderly, may die as a direct or indirect consequence of an influenza infection. Particularly, older people and patients with chronic underlying disease may experience serious complications and become hospitalized. In many cases, these patients are treated for the clinical condition for which they are hospitalized, without recognizing the underlying viral influenza infection which may have exacerbated their condition. Therefore, clinicians may not always recognize the impact influenza infections may have had upon their patients.

For the same reasons, the protective effectiveness of influenza vaccines is difficult to assess based on purely clinical grounds. Many symptoms of influenza infections are similar to symptoms caused by other, non-influenza pathogens. Obviously, influenza vaccines will protect only against disease caused by the influenza viruses and not by other pathogens causing influenza-like illnesses.

Recognizing the annual burden of influenza disease for people and populations, WHO has, since the 1950’s, been maintaining its Global Influenza Surveillance and Response System (GISRS). This group of specialist scientists is tasked with identifying the most commonly circulating influenza viruses and ensuring the best possible antigenic match in the annual influenza vaccines. The GISRS makes recommendations on the appropriate vaccine compositions for both the Northern and the Southern Hemispheres each year. Although antigenic mismatches can occur occasionally, for most years there is a good antigenic match between the epidemic and vaccine strains, indicating the success of this global program.

The method of growing influenza virus, from which to produce a vaccine, in eggs was developed in the late 1940’s and the vaccines so produced have been investigated and used extensively over the last 65 years. Despite the methodological complexities involved in measuring the benefits of the vaccines on society, the safety and efficacy of the vaccines in preventing serious influenza associated complications, hospitalizations and deaths, particularly of the elderly have been extensively documented in the literature. Recommendations of the WHO (1, 2) and other Health Authorities are based on this documented scientific evidence and represent a strong foundation to advocate and implement seasonal influenza vaccination.

Unfortunately, in many countries, inactivated influenza vaccines are seriously under-utilized despite the global and publically driven efforts of WHO and other health organizations and institutes. The documented evidence, as basis for immunization recommendations, is not always fully appreciated and is sometimes debated. As a consequence, many people at-risk of complications associated with influenza infections, such as the elderly and those with chronic conditions, are not vaccinated and afforded potential protection against negative impacts on their health. On a societal level, the burden imposed by these infections and complications represent an avoidable cost for the healthcare system and budget.

Based on such considerations, the World Health Assembly has adopted a resolution calling for a vaccination rate of 75% of the elderly by the year 2010. From available global vaccination distribution data and published uptake rates, these target rates are not yet met in many countries, although over the period 2004–2009, the global vaccine usage increased by 70% to a total volume of 450 million doses. In Europe, new target vaccine uptake rates have been formulated to reach 75% uptake by elderly and at-risk patients in 2015.

Global efforts to improve seasonal influenza prevention in the future

As outlined above and depicted in Figure 1, there is a clear need to improve the level of seasonal influenza prevention in many countries. Improved seasonal influenza control measures, by fully implementing current recommendations, are important for individual at risk patients but also for global, regional and national pandemic preparedness efforts. As the H1N1 pandemic experience has demonstrated, pandemic control is very much linked to existing vaccine- and antiviral production capabilities and existing health infrastructures before the pandemic.
WHO’s Global Action Plan–II (GAP–II)

In 2006, the WHO launched its first Global Action Plan (GAP-I) in anticipation of an emerging pandemic. In 2011, the WHO started a consulting procedure to define its follow-up Global Action Plan for the next 5 years (GAP-II). Increasing uptake rates of seasonal influenza vaccines is one of the three main pillars of the GAP program with the aim to respond to the direct need of annual disease prevention for patients and society as well as indirect needs to be better prepared for future pandemics.

One of WHO’s key GAP-I objectives was to facilitate and support initiatives to create local influenza vaccine production capacity in some developing countries. Today, such facilities have been realized in countries such as Thailand, Korea, India, and Indonesia.

It is of interest to note that, in many of these countries, the distribution rates of seasonal influenza vaccines are low. To achieve the full benefits of these local production facilities at a future influenza pandemic, it is important that these facilities routinely produce influenza vaccines in volumes which are relevant for pandemic containment. The WHO-recommended increased seasonal vaccination uptake rates will provide a realistic economic basis for the new production facilities to be sustainable.

Global Pandemic Influenza Preparedness Framework Agreement (PIPFA)

In addition to WHO’s GAP-II program, an international agreement was reached in 2011 between WHO, World health Assembly member states and industry to ensure global “sharing of influenza viruses and access to vaccines and other benefits” to strengthen the global infrastructure for pandemic influenza preparedness. As part of this process, WHO’s GISRS will be strengthened and access to pandemic vaccines for middle- and low income countries will be secured, according to the principles laid down in the global Pandemic Influenza Preparedness Framework Agreement.5

Factors to understand the influenza paradox and examples for solutions

Although recommendations and global initiatives are indispensible to guide and
drive health programs, the success of these programs heavily depend on their acceptance and implementation in countries by the relevant stakeholders. If influenza is often poorly recognized and considered a "hidden disease", one can easily understand the barriers to fully comply with the vaccination recommendations and the programs to increase vaccine uptake rates. It seems that there is a gap between well documented epidemiological and vaccine data and the personal "experience" of physicians and at risk individuals. It seems apparent that awareness and knowledge of the annual burden of influenza disease in specific population segments and the benefits and (minimal) risks of the vaccines may not be sufficiently high in important groups such as policy makers, nurses, physicians and the 'at risk' patient populations.

Many studies have been done to understand factors contributing to the phenomenon of the "influenza paradox". A number of these factors appear to be perceptions about the disease and the vaccines which are often not based on evidence, but merely on subjective opinions and behavior patterns.

In a sub-analysis of a recently reported study on the influenza vaccine distribution rates in 157 countries, it was found that reimbursement for patients and public awareness campaigns and communications by national Health Authorities were the two policy actions which were highly correlated with vaccine distribution rates. Formal recommendations per se, although a prerequisite to support vaccination campaigns, were not found to be correlated with vaccine distribution rates.

**Healthcare workers and influenza prevention**

In many countries in Europe and most likely in other countries as well, at risk individuals are vaccinated if advised by their physicians. Hence, these healthcare providers are instrumental for the implementation of programs to increase vaccine uptake rates. Global, regional and national efforts to achieve these goals should therefore be a focus of both, education about the disease and its control measures as well as behavioral aspects.

Healthcare workers are included in many of the existing vaccination commendations by WHO and national Health Authorities. Vaccine uptake rates in healthcare workers have increased in recent years, particularly in the USA. However, generally speaking, in many countries there is not yet an acceptable level of vaccination amongst these professionals which bear a special responsibility for patients' safety.

As influenza infections belong to the group of nosocomial infections, there is an increased tendency, particularly in the USA, to consider influenza vaccination for employees as a patient safety consideration. Many programs and initiatives have been tried in institutions to increase vaccination rates amongst healthcare workers on a voluntary basis. In general, these efforts had some positive effect, and stimulated uptake rates somewhat but not to acceptable levels and many times the results were not sustainable. Today, an increasing number of healthcare institutions in the USA are taking a leadership position and require their employees to be vaccinated against influenza as part of the internal infection control and institutional quality programs.

**Link between International health initiatives and influenza immunizations**

Recently, a number of important global health initiatives were initiated such as the Global Action Plan for Non-Communicable Diseases (NCDs) which primarily focus on diabetes, respiratory illness, cardiac disease and cancer. In addition, there are various initiatives looking at maternal and child health as well as healthy aging. Although these initiatives are not focused on influenza disease, annual immunizations against influenza infections fit very well with the overall objectives of these health programs.

Patients with diabetes, acute and chronic respiratory disease, cardiac disease and the elderly in general, are all known to be at increased risk of influenza infections which often can provoke deterioration of their underlying medical conditions. Influenza immunization of these patients, according to current recommendations will therefore protect these vulnerable patients against influenza-induced disease and exacerbations of their underlying disease. Thus, annual influenza prophylaxis will contribute to the positive management of these important non-communicable diseases and contribute to health initiatives to address these diseases and promote healthy aging. Incorporating influenza immunization into these programs could protect patients and reduce the overall burden on healthcare systems.

**Conclusion and Recommendations**

Despite the availability of safe and effective influenza vaccines and independent recommendations for their use by WHO and other Public Health Authorities, influenza still constitutes a "preventable disease not being prevented".

The successful implementation of global efforts and initiatives to increase seasonal vaccine uptake rates and pandemic preparedness depends on alignment of all respective stakeholders at national and local levels.

Educational programs, public campaigns of independent health authorities, reimbursement and institutional leadership to promote influenza prophylaxis will be beneficial to patients and society and support global and national efforts for pandemic preparedness and contribute to public health. Countries within the Asian region have a real opportunity to successfully implement effective influenza immunization programs early-on and leverage many of the public health studies and experiences which are available today.
Dr. Palache (1952) is currently Global Government Affairs Director, Vaccines at Abbott Biologicals (formerly Solvay) in Weesp, the Netherlands.

Dr. Palache received his MSc degree in Biochemistry at the University of Amsterdam in 1980. After graduation, he initiated his professional career as a Clinical Research Associate at Solvay Pharmaceuticals in the Netherlands. He gained a lot of experience in clinical development of new drugs in various fields. Prior to his current position, he held different ‘Clinical Group-leader’ functions. In such position he directed the clinical development program of Solvay’s new cell-cultured influenza vaccine (MDCK), which was registered in 2001 in the Netherlands.

He was an Influenza Research Fellow at the Dutch National Influenza Centre: Erasmus University, Rotterdam (chair: Professor A. Osterhaus), where he received his PhD in Medical Science in 1991.

He is a co-founder of the European Scientific Working Group on Influenza (ESWI, 1992).

Since 2001, he is member of the Public Health Working Group of the Association of the European Vaccine Manufacturers (EVM) and in 2005, he joined the Influenza Working Group, which he co-chairs since January 2009.

In 2003, he became founding member of the Influenza Vaccine Supply International Task Force (IVS) and since 2004, he chairs the Policy Practice and Communication subgroup (PPC) of the IVS. In 2006, he joined the APACI (Asian Pacific Advisory Committee Influenza) group as Solvay Biologicals representative.

Dr. Palache is the author of over 50 papers most of which were published in peer-reviewed medical scientific journals. He is co-author of the Rapid Reference book Influenza which is published by Elsevier in 2006 and has been translated in four languages.
Circadian Technologies Limited announced that it has commenced the first Phase 1 clinical trial of its fully human monoclonal antibody against VEGF-C, VGX-100, at a leading US-based cancer treatment centre.

The Phase 1 study will examine the safety and tolerability of escalating doses of VGX-100 in patients with advanced solid tumours who have no other standard treatment options both as a monotherapy and also when used in combination with other anti-angiogenic agents. Results from the trial are expected to be available in the second half of 2012.

“We are extremely proud to have completed the translation of VGX-100 from early discovery to the clinical development stage. We are committed to improving outcomes for patients suffering from cancer, and believe that VGX-100, especially when combined with existing therapies could make a significant difference. Commencing clinical trials with VGX-100 is an extremely important achievement for Circadian and a major step in our goal to develop VGX-100 as a new therapeutic agent in the fight against cancer,” said Robert Klupacs, CEO of Circadian Technologies Limited.

VGX-100 is a human antibody that acts against the human VEGF-C protein. Treatment for cancers, particularly glioblastoma and metastatic colorectal cancers, are the first target indications for VGX-100. Additionally, Circadian is developing VGX-100 for a number of other cancer indications, as well as an agent to treat front-of-the-eye diseases.

Studies in animal model studies across a wide range of tumour types have shown that when combined with Avastin and/or chemotherapy, VGX-100 can significantly reduce tumour growth and tumour spread as well as significantly improve tumour inhibition over and above that of Avastin and/or chemotherapy alone. Recent studies have also implicated VEGF-C as a key mediator of disease progression during Avastin treatment, implying that combination therapy with VGX-100 and Avastin could significantly improve treatment outcomes in cancer patients.

Circadian’s wholly owned subsidiary, Vegenics Pty Ltd, owns worldwide rights to an extensive intellectual property portfolio covering the angiogenesis and lymphangiogenesis targets VEGF-C, VEGF-D and the receptor protein VEGFR-3. Vegenics has also been granted exclusive worldwide rights to intellectual property filed by Schepens Eye Research Institute covering the use of anti-lymphangiogenic molecules for the treatment of Dry Eye Disease.
Life Technologies Partners With DaAn Gene to Develop and Commercialize Molecular Diagnostic Assays in China

Life Technologies Corporation LIFE +0.02% announced that it has signed an agreement with DaAn Gene, a leading Chinese company in molecular in-vitro diagnostics (IVD), to form Life Technologies DaAn Diagnostics, a joint venture diagnostics business in China. The move is expected to contribute to the early diagnosis of oncology, infectious diseases and genetic diseases. Financial terms of the deal were not disclosed.

Life Technologies DaAn Diagnostics with its headquarters in Guangzhou, will develop and commercialize a portfolio of molecular diagnostic assays using Life Technologies’ 3500Dx Capillary Electrophoresis instrument and the Big Dye Cycle Sequencing technologies, focused on IVD assays for oncology, infectious and genetic diseases. The joint venture allows both companies to expand the use of Capillary Electrophoresis technology into the Chinese clinical diagnostics market.

“This joint venture strengthens the foundation of our clinical diagnostics business and represents a big leap forward for our business in China,” said Gregory Lucier, Chairman and CEO of Life Technologies. “As a leading biotechnology company, we are at the forefront of a rapidly evolving healthcare landscape. This joint venture and its products will play a key role in disease prevention and therapy selection and is complementary to the Chinese government’s 12th five-year plan to promote national economic and social development.”

“The joint venture will help us offer leading medical diagnostic technologies with cost-effective solutions to Chinese healthcare professionals,” said Dr. Siddhartha Kadia, President of Life Technologies, Greater China. “This approach leverages our expertise in platform development and DaAn’s expertise in regulated markets with kit development and commercialization.”

“Twenty years ago, the cooperation between DaAn and Applied Biosystems brought PCR technology into China’s molecular diagnostic field, positioning China with the most potential to become the world’s largest PCR market for clinical diagnostics. Today, the cooperation with Life Technologies introduces DaAn’s products to the global marketplace, while bringing Life’s superior technologies into China’s IVD market. Together, we are working toward becoming a premium IVD product supplier that has global impact,” said Zhou Xinyu, CEO of DaAn Gene.

Life Technologies’ 3500Dx instrument is a capillary-based Sanger Sequencer intended for use in the analysis of human DNA for the detection of genetic changes that may lead to disease presence or improved response to various therapies. Life Technologies’ Sanger Sequencers supplied the technology that powered the Human Genome Project. Sanger instruments remain the sequencing gold-standard for accuracy, reliability and ease of use. The 3500Dx Genetic Analyzer was approved by China State Food and Drug Administration (SFDA) for IVD diagnostic use in China in October 2011.
Doctors at BGS Global Cancer Institute at BGS Global Hospitals in Bangalore have begun delivering advanced radiotherapy treatments using the first clinical TrueBeam STx medical linear accelerator in Asia. A 57-year-old female patient with a brain metastasis received whole brain radiotherapy and this will be followed by stereotactic radiosurgical boosts to the lesion using the fast and precise system.

“The whole procedure, the imaging and treatment, was completed within five minutes,” says Dr. Nirmala Srikantia, senior consultant and chief of radiation oncology services at BGS Global Cancer Institute. “TrueBeam STx gives our oncologists the flexibility to deliver multiple high precision treatments such as this while minimizing the time required and, potentially, the inconvenience to the patient.”

“The new system’s advantages of speed and precision will help benefit our patients in receiving timely treatments. Our specialists will be able to offer high quality treatments to more patients and deliver them more quickly than has been possible in the past,” adds Dr. Srikantia.

Designed to advance the treatment of lung, breast, prostate, gynaecologic, liver, head and neck, and other types of cancer, the TrueBeam platform from Varian Medical Systems was engineered from the ground up to treat tumors with unprecedented speed and accuracy. It features a multitude of technical innovations that dynamically synchronize imaging, patient positioning, motion management, and treatment delivery. With its High Intensity Mode, TrueBeam machines can deliver very high doses quickly and accurately, more than twice as fast as earlier generations of technology. The TrueBeam STx is a high-end model optimized for radiosurgical applications, where very large doses are delivered in a single treatment or only a few sessions.

Initial TrueBeam STx treatments at BGS Global Hospitals will focus on brain, head and neck, gastro-intestinal and gynaecologic cancers using advanced techniques such as IMRT (intensity modulated radiotherapy). The team intends to commence stereotactic radiosurgery treatments. “Since the hospital was established, our specialists have routinely treated various types of cancers using medical oncology and surgery, but the TrueBeam STx means we can now offer advanced radiosurgery treatments in addition,” says Dr. K. Ravindranath, chairman and managing director of Global Hospitals Group.

Global Hospitals has acquired three TrueBeam STx systems – ordered in 2010 – for its sites in Bangalore, Chennai and Mumbai, because of the rapidly increasing cancer incidence in these major population centers, along with the strength of the neuroscience departments in those hospitals. “This will make some of the world’s most advanced treatment capabilities accessible for cancer patients in these major Indian cities,” adds Dr. Ravindranath. “This country needs more radiotherapy equipment to help its cancer patients and we believe we can help relieve this situation by installing the most modern and advanced devices available.”

Rolf Staehelin, international head of marketing operations for Varian’s Oncology Systems group, says, “Varian is at the forefront in offering advanced systems for radiosurgical and neurosurgical treatments in India and we are delighted to be working closely with Global Hospitals Group as they introduce this ground-breaking technology for the benefit of cancer patients.” India has a population of over a billion people and there are an estimated one million new cases of cancer diagnosed in the country each year.
Lancaster Laboratories and BioAzure Enter Partnership

U.S.-based Lancaster Laboratories, a Eurofins Scientific company, and Mumbai-based BioAzure Technologies have announced a partnership to provide Lancaster Laboratories’ contract laboratory services to the Indian biotech market in support of product development regulatory compliance goals.

A global leader in comprehensive laboratory services, Lancaster Laboratories enables pharmaceutical and biopharmaceutical companies to advance candidates from development through to commercialization while ensuring regulatory compliance, cost effectiveness, and achievement of timelines. The company provides an unmatched breadth of GMP and GLP services, including protein characterization, cell bank testing, viral clearance studies and method validation to clients around the world, including some of the world’s largest biotechnology companies.

“With the progress of India’s significant biotechnology presence, including its focus on biosimilars and biobetters, Lancaster Laboratories looks forward to working closely with BioAzure to enable Indian biotech companies to achieve their regulatory compliance objectives for their product development and manufacturing activities,” says Timothy S Oostdyk, PhD, president of Lancaster Laboratories. “With the goal of delivering a seamless service experience, we plan to focus on ways to customize our service models to cater specifically to Indian companies. We expect this part of our business to grow rapidly, along with the Indian biotech industry.”

Commenting on the partnership, Dr Adrian Almeida and Karl Pinto, co-founders of BioAzure stated, “Working with Lancaster Laboratories enables BioAzure to provide a complete spectrum of solutions to our biotech clients here in India. BioAzure was founded with the intent of supporting Indian biotech from in-licensing cell line clones to scale-up process development and GMP manufacturing along with complete regulatory-approved analytics and formulation capability through our exclusive relationships with name-brand, world class companies in this space.”
NovAliX announced that it has entered into a multi-target integrated drug discovery collaboration with Teijin Pharma Limited of Tokyo, Japan.

Within the alliance the companies will collaborate to develop novel drug candidates against multiple targets across different therapeutic areas. NovAliX will initially use its protein biochemistry expertise in combination with its comprehensive biophysical technology platform. NovAliX will apply its proprietary Graffinity SPR-based screening technology for the identification of novel chemotypes, and then engage its native nano-MS technology for further characterization of selected small molecule hit structures.

This arrangement represents NovAliX’s first discovery collaboration with Teijin Pharma. Under the terms of the agreement, NovAliX will receive technology access fees as well as further research funding payments. Financial details of the transaction were not disclosed.

Stephan Jenn, President of NovAliX, stated, “We are confident that this alliance will be very productive and are proud to be associated with Teijin’s technology-driven team. In this collaboration Teijin will have the opportunity to leverage the entire spectrum of our capabilities in biochemistry, biophysics and medicinal chemistry. For NovAliX this integrated collaboration represents a significant milestone as Teijin is the second Japanese pharmaceutical company to partner with us this year. This alliance underlines again the competitive edge of our scientific expertise and biophysical technologies as well as our commitment to serve the Japanese pharmaceutical research market that is strongly driven by science and innovation.”
Otsuka Pharmaceutical Co., Ltd. and UCB announced that the companies have agreed to focus their collaboration on the therapeutic area of Central Nervous System (CNS) disorders and to discontinue their collaboration in immunology.

The companies will end their co-development and co-promotion agreement for certolizumab pegol in Japan followed by an agreed upon transition period.

UCB is preparing to file certolizumab pegol for marketing authorisation with the Japanese Ministry of Health, Labour and Welfare (MHLW) in the first quarter of 2012. Positive Japanese Study Results, showing that certolizumab pegol was associated with significant inhibition of structural joint damage progression and significant improvements in physical function compared to placebo, were published at the recent American College of Rheumatology’s (ACR) 2011 Annual Scientific Meeting.

The decision to discontinue its collaboration in immunology is in line with Otsuka Pharmaceutical’s clear priorities to focus in the future on CNS and oncology in its pharmaceutical business.

In December 2011, Otsuka Pharmaceutical filed rotigotine for marketing authorisation in Japan with the MHLW for the treatment of Parkinson’s disease and restless legs syndrome. In 2010, E Keppra (levetiracetam), was approved and launched in Japan for the adjunctive treatment of partial onset seizures in adults with epilepsy which offers many patients a new option of treatment.

"Otsuka will strengthen the partnership with UCB in Japan while focusing on CNS compounds such as E Keppra, an anti-epileptic drug, and rotigotine, a dopamine agonist patch," said Dr. Taro Iwamoto, President and Representative Director of Otsuka Pharmaceutical Co., Ltd. "we remain dedicated to maximising the value of these two compounds while continuing to investigate additional indications. Otsuka and UCB will build a strong sales base so that our compounds can positively contribute to a number of patients in need."

“We are happy to continue our successful partnership with Otsuka Pharmaceutical in the area of CNS, namely E Keppra and rotigotine.” said Mark McDade, Executive VP, Chief Operating Officer, UCB. “And in the interest of Japanese patients living with severe immunological disorders, UCB is committed to building on the franchises of the immunology therapeutic area in Japan starting with certolizumab pegol.”
BIOTRONIK, a leading manufacturer of high quality products for vascular intervention, implantable cardiac pacemakers and defibrillators, and the pioneer of wireless remote monitoring technology, announced the opening of a new regional headquarters location based in Singapore—a move that emphasizes the strategic commitment of the company to build a powerful leadership position in the Asia Pacific region.

BIOTRONIK is a global enterprise that has achieved consistent double-digit growth in revenue during the last seven years, as well having doubled its job opportunities for employees. In Asia Pacific alone, BIOTRONIK has tripled its revenue over the last five years and employs more than 250 representatives. Further short-term growth is expected to be driven by a broadly expanded service network, as well as new and innovative product introductions such as the Orsino, the company’s unique hybrid drug-eluting stent technology for coronary vascular intervention, and Lumax 740, the first ProMRI ICD in the market, for patients with tachycardia heart rhythm disorder.

“BIOTRONIK will fully leverage the accelerated development of the Asia Pacific countries to further propel the industry-leading growth trajectory that the company has maintained during previous years despite the global economic downturn,” commented Dr. Werner Braun, Global Managing Director, BIOTRONIK. “The economic independence of BIOTRONIK has allowed us to deliver a uniquely sustainable value proposition to our customers—one that includes investment in activities, such as our landmark clinical research program and best-in-class clinical education—in an environment where we have seen our competitors de-investing.”

Braun continued, “Our further plans for full-scale business development in Asia Pacific, which will be coordinated by a highly professional team based out of the new headquarters in Asia, are the latest milestone of many more to come for BIOTRONIK and our customers in this region.”

“BIOTRONIK is one of the leading cardiovascular companies in the world, and we are proud BIOTRONIK has chosen Singapore to be its Asia Pacific headquarters. Singapore, with its strong regional connectivity and talent base, is well positioned as the strategic base to help companies access, manage and grow the diverse Asia Pacific market,” said Mr. Kevin Lai, Deputy Director, Biomedical Sciences, Singapore Economic Development Board.
A*STAR, GE Global Research Join Forces to Develop Integrated Advanced Medical Imaging Technologies for Improved Clinical Diagnosis

GE Global Research, the central technology development arm for GE Healthcare and all of GE’s businesses, has signed a Memorandum of Understanding (MOU) with Singapore’s Agency of Science, Technology and Research (A*STAR). This agreement will focus on advancing current medical imaging technologies and diagnostics to enable more accurate, earlier and faster clinical diagnoses of cancer and other diseases. The partnership between A*STAR and GE Global Research brings together two world-class research institutions, integrating their deep domain expertise in biomedical, science, and engineering capabilities to support this effort.

This MOU expands upon a productive collaboration between GE and A*STAR’s Singapore Bioimaging Consortium (SBIC) using Hyperpolarized Carbon-13 technology. Early results exploring sub second biochemical imaging in Oncology applications helped pave the way for a broader scientific collaboration on projects in medical diagnostics and medical imaging. The goal is to improve diagnosis and tissue characterization in diseases that are prevalent in the Asian population, such as liver, lung, and gastric cancers.

Michael Idelchik, Vice President of Advanced Technology Programs at GE Global Research, said, “To more effectively combat cancer and other deadly diseases, more advanced diagnostic tools will be needed to help doctors become more prescriptive in their diagnoses and treatment regimens. Combining A*STAR’s world-class biomedical and clinical expertise with GE’s strengths in diagnostic and molecular imaging, we have an exciting opportunity to take medical diagnosis to this next level. Specifically, A*STAR will help us address cancers and other diseases more common in Asia and where pathology and outcomes are different as compared to the rest of the world.”

Professor Low Teck Seng, Managing Director of A*STAR, said, “This win-win public-private partnership between A*STAR and GE comes at an opportune time with the increasing research interest in diseases affecting the Asian population. I am confident that A*STAR’s cross-disciplinary capabilities in both the biomedical, and physical sciences & engineering research will complement GE’s expertise in diagnostic and molecular imaging to meet today’s complex healthcare challenges and enhance lives.”

As part of the MOU, A*STAR and GE Global Research will collaborate to enhance medical imaging technologies in imaging modalities, ranging from magnetic resonance imaging (MRI) and positron emission tomography (PET) to computed tomography (CT). In a Frost & Sullivan global market analysis report, the medical imaging sector was valued at about US$25 billion as of 2008, with MRI and CT scanners accounting for a combined 40% of the total global device medical imaging market. In one project, scientists from A*STAR’s Institute of Microelectronics (IME) and GE scientists will explore the development of new imaging technologies to improve the speed and accuracy of clinical cancer diagnosis. Leveraging IME’s network and partnerships with the microelectronics industry, this project could result in the development of a new local industry for Singapore in the healthcare technologies area.

In another project, A*STAR’s Singapore Bioimaging Consortium (SBIC) and GE plan to develop novel imaging markers for hepatic cellular carcinoma (HCC), the most common type of liver cancer in Asia. This project will integrate biomedical imaging and pre-clinical model development expertise from SBIC with GE’s molecular diagnostics technology to develop innovative, proprietary platforms to help advance the unique characterization of HCC in each patient. In this manner, the goal is that a specific type of cancer would be identified and the therapy tailored to each patient. This project encompasses a range of medical diagnostic technologies from imaging to molecular pathology biomarkers appropriate to HCC, relevant to the Asian population. Building on a close partnership with local hospitals, success in this project may lead to accelerated and accurate cancer diagnosis that enables more prescriptive and effective cancer treatments for patients. This will support A*STAR’s efforts to develop Singapore as a Center for Oncology and Molecular Pathology.
Alpha to Build $50m Plant in Thailand

Alpha Group Holdings, a China-based biotech company, plans to build a US$50-million manufacturing facility in Thailand over the next two years to capitalize on Thai herbs.

Headquartered in Auckland, Alpha Group operates manufacturing facilities in China, New Zealand and Australia for health supplements, functional food and skin-care products. Its subsidiaries operate in 19 countries including Hong Kong, Korea, Taiwan, Macau, the US and Canada.

Singapore, Malaysia, Burma and Thailand are major markets for Alpha, as Asean generates one-third of the company's turnover or about $750 million last year. Indonesia is considered a high-potential market given its population.

Thailand is famous for natural herbs in provinces such as Chiang Mai and Chiang Rai.

"We are considering having a plant in Asean, perhaps in Thailand or Burma, but Thailand is our priority, as the market for weight-loss products and male sex performance enhancers is growing. We will start with a research center first and spend a couple years for market development since we are new in Thailand," said Mr Wei Gao, Alpha chief executive, as he visited Bangkok with a group of Chinese government officials and trade associations to mark the 20th year of China-Asean economic relations.

"The Thai plant will be a manufacturing centre for Asean, enabling lower costs and the benefits of free-trade agreements," Mr Wei added. Alpha Bio-Technology started distributing products in Thailand last year, all imported from New Zealand, resulting in high transportation costs.
A STAR scholar, Ms Christine Cheung was the first author of a Nature Biotechnology paper published this month. The Cambridge team has for the first time, discovered a method of generating different types of vascular smooth muscle cells (SMCs) – the cells which make up the walls of blood vessels - using cells from patients’ skin. This work could lead to new treatments and better screening for cardiovascular disease.

Cardiovascular disease is the leading cause of death in the world. It also accounts for one in three deaths each year in Singapore. These deaths are mainly caused by the hardening and subsequent blockage of blood vessels due to the accumulation of fatty materials, a condition called atherosclerosis. As not all patients are suitable for conventional stenting or bypass treatment, an option in the future may be to grow new blood vessels to bypass their own blocked vessels.

The team from the University of Cambridge worked with embryonic stem cells and reprogrammed skin cells, collectively known as human pluripotent stem cells (hPSCs), which have the potential to form any cell type in the body. They discovered a method of creating all the major vascular smooth muscle cells in high purity using hPSCs which can also be easily scaled up for production of clinical-grade SMCs. This is the first time that such a system has been developed and will open the door for comparative studies on different subtypes of SMCs to be carried out, which are otherwise extremely difficult to obtain from patients.

The scientists created three subtypes of SMCs from different embryonic tissues which they reproduced in the culture dish and showed that the various SMC subtypes responded differently when exposed to substances that cause vascular diseases. They concluded that differences in the embryonic origin play a role in their susceptibility to diseases and may play a part in determining where and when common vascular diseases such as aortic aneurysms or atherosclerosis develop.

Dr Alan Colman, Principle Investigator of the Institute of Medical Biology under A*STAR and Executive Director of the Singapore Stem Cell Consortium, said, “This is a major advance in vascular disease modelling using patient-derived stem cells. The development of robust methods to make multiple, distinct smooth muscle subtypes provides tools for scientists to model and understand a greater range of vascular diseases in a culture dish than was previously available. It is a significant stride forward in being able to construct new blood vessels which will benefit a whole range of patients including those with cardiovascular diseases, renal failure and genetic disorders such as Marfans Syndrome that affect the normal function of their blood vessels.”

Dr Lim Khiang Wee, Executive Director of the A*STAR Graduate Academy (A*GA), said, “Christine’s work reflects the calibre of our scholars – they do excellent research and grow into scientists who will contribute to Singapore when they return.”

Ms Christine Cheung is a National Science Scholarship (NSS) scholar and is doing her final year PhD studies at Cambridge University (UK). The NSS scholarship is one of the programmes offered by A*GA, to attract and develop outstanding young talent passionate about research who will spearhead Singapore’s drive to becoming Asia’s Innovation Capital.
Singapore Scientists Identify Lung Cancer Stem Cells and New Drug Targets

Singapore scientists, headed by Dr Bing Lim, Associate Director of Cancer Stem Cell Biology at the Genome Institute of Singapore (GIS), a research institute under the umbrella of the Agency for Science, Technology and Research (A*STAR), and Dr Elaine Lim, medical oncologist affiliated with Tan Tock Seng Hospital (TTSH) and National Cancer Centre Singapore (NCCS), have for the first time, identified a gene responsible for lung cancer. The finding, reported in the advanced online issue of Cell on 5 January 2012, is a huge step towards finding a cure for the disease.

A small number of cells, known as cancer stem cells or tumor-initiating cells (TIC), are responsible for the promotion of tumor growth. Dr Bing Lim’s team was successful in finding a marker, known as CD166, to identify these cells. With the finding of this marker, the team then made more inroads into the genomics of the TICs, and discovered several genes that were important for the growth of cancer cells.

The metabolic enzyme known as glycine decarboxylase (GLDC) is a normal occurring enzyme in cells, present in small quantities. The scientists discovered that in abnormal instances when the level of GLDC rises significantly, it causes changes in the behavior of the cell, making it cancerous.

“This manuscript from Dr Bing Lim’s laboratory provides a very exciting breakthrough about the unique metabolism of tumor initiating cells” said Dr Lewis Cantley of Harvard Medical School. “This study builds on recent observations that a subset of cancer cells have enhanced serine/glycine metabolism. Importantly it shows that the enzyme glycine decarboxylase, which contributes to nucleotide synthesis, is elevated in lung tumor initiating cells and that it is critical for the ability of these cells to form tumors in vivo. Since glycine decarboxylase does not appear to be generally required for the growth of normal adult tissues, these results raise the possibility that this enzyme could be a target for cancer therapy.”

“This research is exemplary of the synergy between cancer researchers and clinicians that led to a breakthrough in our understanding of the metabolic pathway in lung cancer. I congratulate Dr Bing Lim and Dr Elaine Lim for leading this impressive multi-institutional study,” said Dr Huck Hui Ng, Acting Executive Director of GIS. “The discovery of the biomarker has profound implications in cancer diagnostics and stratified medicine. It is hopeful that the metabolic enzyme GLDC will be a good target for drug development by the pharmaceutical industries.”

Dr Bing Lim added “This is one of the most satisfying pieces of work I have orchestrated and the biggest credit must go to my post doctoral fellow, Dr Wen Cai Zhang, who took the project from first establishing a xenograft model for human lung cancer to the identification of CD166 as a marker for lung cancer stem cell and culminating with the amazing discovery of the impact of a regular metabolic enzyme in carcinogenesis. It is doubly satisfying that we may have also identified a major drug target for controlling cancers”.

Dr John Wong, Vice Provost (Academic Medicine) of the National University of Singapore, explained that “Lung cancer is one of the most common causes of cancer death in Singapore and the region. There is an urgent need to better understand what drives this disease, especially as lung cancer in Asians appears to have major biological differences compared to that commonly seen in the West. The authors of this seminal paper should be congratulated as they represent the best of Team Science in Singapore, comprising both basic scientists and clinician investigators, all working to develop better therapies for Singaporeans and the community we live in. The findings from Dr Bing Lim’s team strongly support the cancer stem cell paradigm and similar studies in other cancers need to be done.”

Elaine Lim, co-corresponding author and co-principal investigator in this project said, “This paper is the result of successful co-operation between scientists and doctors from the Singapore Lung Cancer Consortium, with the Stem Cell division in GIS. The thoracic surgeons from TTSH, NCCS and NUHS have made outstanding contributions to this homegrown scientific project.”

Prof Soo Khee Chee, Director of NCCS, said that “NCCS has made important contributions to medical research through the years, both in clinical as well as basic research. This paper is an example of a very satisfying outcome when medical doctors and scientists huddle together to produce high-quality work. Co-operation between seemingly disparate disciplines amongst the different institutions in Singapore, led by Elaine and Bing, was critical to this success – and there will be many more to come”.

“This study has made significant contributions to our fundamental understanding of lung cancer,” added Prof Philip Choo, Chief Executive Officer at TTSH. “The study also represents an exceptional step forward for medical research involving doctors and scientists. We look forward to more of such collaborative efforts in the future.”
T-rays Technology Could Help Develop Star Trek-Style Hand-held Medical Scanners

T-rays technology could help develop Star Trek-style hand-held medical scanners. Scientists who have developed a new way to create a type of radiation known as Terahertz (THz) or T-rays - the technology behind full-body security scanners - say their new, stronger and more efficient continuous wave T-rays could be used to make better medical scanning gadgets and may one day lead to innovations similar to the “tricorder” scanner used in Star Trek.

In a study published recently in Nature Photonics, researchers from the Institute of Materials Research and Engineering (IMRE), a research institute of the Agency for Science, Technology and Research (A*STAR) in Singapore and Imperial College London in the UK have made T-rays into a much stronger directional beam than was previously thought possible and have efficiently produced T-rays at room-temperature conditions. This breakthrough allows future T-ray systems to be smaller, more portable, easier to operate, and much cheaper.

The scientists say that the T-ray scanner and detector could provide part of the functionality of a Star Trek-like medical “tricorder” - a portable sensing, computing and data communications device - since the waves are capable of detecting biological phenomena such as increased blood flow around tumorous growths. Future scanners could also perform fast wireless data communication to transfer a high volume of information on the measurements it makes.

T-rays are waves in the far infrared part of the electromagnetic spectrum that have a wavelength hundreds of times longer than visible light. Such waves are already in use in airport security scanners, prototype medical scanning devices and in spectroscopy systems for materials analysis. T-rays can sense molecules such as those present in cancerous tumours and living DNA as every molecule has its unique signature in the THz range. T-rays can also be used to detect explosives or drugs, in gas pollution monitoring or non-destructive testing of semiconductor integrated circuit chips. However, the current continuous wave T-rays need to be created under very low temperatures with high energy consumption. Existing medical T-ray imaging devices have only low output power and are very expensive.

In the new technique, the researchers demonstrated that it is possible to produce a strong beam of T-rays by shining light of differing wavelengths on a pair of electrodes - two pointed strips of metal separated by a 100 nanometre gap on top of a semiconductor wafer. The unique tip-to-tip nano-sized gap electrode structure greatly enhances the THz field and acts like a nano-antenna that amplifies the THz wave generated. The waves are produced by an interaction between the electromagnetic waves of the light pulses and a powerful current passing between the semiconductor electrodes from the carriers generated in the underlying semiconductor. The scientists are able to tune the wavelength of the T-rays to create a beam that is useable in the scanning technology.

Lead author Dr Jing Hua Teng, from A*STAR’s IMRE, said: “The secret behind the innovation lies in the new nano-antenna that we had developed and integrated into the semiconductor chip.” Arrays of these nano-antennas create much stronger THz fields that generate a power output that is 100 times higher than the power output of commonly used THz sources that have conventional interdigitated antenna structures. A stronger T-ray source renders the T-ray imaging devices more power and higher resolution.

Research co-author Stefan Maier, a Visiting Scientist at A*STAR’s IMRE and Professor in the Department of Physics at Imperial College London, said: “T-rays promise to revolutionise medical scanning to make it faster and more convenient, potentially relieving patients from the inconvenience of complicated diagnostic procedures and the stress of waiting for accurate results. Thanks to modern nanotechnology and nanofabrication, we have made a real breakthrough in the generation of T-rays that takes us a step closer to these new scanning devices. With the introduction of a gap of only 0.1 micrometers into the electrodes, we have been able to make amplified waves at the key wavelength of 1000 micrometers that can be used in such real world applications.”

The research was led by scientists from A*STAR’s IMRE and Imperial College London, and involved partners from A*STAR Institute for Infocomm Research (I2R) and the National University of Singapore. The research is funded under A*STAR’s Metamaterials Programme and the THz Programme, as well as the Leverhume Trust and the Engineering and Physical Sciences Research Council (EPSRC) in the UK.
In a startling medical breakthrough, scientists in Scotland have created brain tissue from skin samples of patients who are suffering from mental illnesses such as schizophrenia and depression.

The latest achievement was made by researchers at Edinburgh’s Centre for Regenerative Medicine.

“A patient’s neurones can tell us a great deal about the psychological conditions that affect them, but you cannot stick a needle in someone’s brain and take out its cells,” the Daily Telegraph quoted Professor Charles ffrench-Constant, the center’s director, as telling the Guardian.

“However, we have found a way round that. We can take a skin sample, make stem cells from it and then direct these stem cells to grow into brain cells. Essentially, we are turning a person’s skin cells into brain,” he stated.

The scientists hope that studying these manufactured brain cells will reveal clues to the conditions of patients with mental illnesses – a task that had been challenging in the past.

“It is very difficult to get primary tissue to study until after a patient has died,” said the Royal Edinburgh Hospital’s Professor Andrew McIntosh, who is collaborating with the center on the project.

“Even then, that tissue is affected by whatever killed them and by the impact of the medication they had been taking for their condition, possibly for several decades. So having access to living brain cells is a significant development for the development of drugs for these conditions,” McIntosh added.

If successful, the same methods could be used for other organs, including the liver and heart.
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<td>2 – 5 Feb</td>
<td>70th All India Ophthalmological Society Annual Conference</td>
<td>New Delhi, India</td>
<td>Dr. A. K. Singh</td>
<td>Tel: +91 11 484 231 6791, Email: <a href="mailto:aios2012@gmail.com">aios2012@gmail.com</a>, URL: <a href="http://www.aios.org/annualconf.asp">http://www.aios.org/annualconf.asp</a></td>
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<td>3 – 5 Feb</td>
<td>3rd International Conference on Current Trends in Forensic Sciences, Forensic Medicine &amp; Toxicology</td>
<td>Jaipur, India</td>
<td>Dr. Ramesh Kumar Sharma</td>
<td>Tel: +91 989 109 8542, Email: <a href="mailto:rksharma1@gmail.com">rksharma1@gmail.com</a>, URL: <a href="http://www.iamleconf.in/home">http://www.iamleconf.in/home</a></td>
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<td>3 – 5 Feb</td>
<td>The 6th Asian-Pacific Congress of Heart Failure</td>
<td>Chiang Mai, Thailand</td>
<td>Dr. N. S. Nagarajan</td>
<td>Tel: +91 944202933, Email: <a href="mailto:icbam2012@gmail.com">icbam2012@gmail.com</a>, URL: <a href="http://www.icbam2012.com">www.icbam2012.com</a></td>
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<tr>
<td>9 – 11 Feb</td>
<td>EMS 2012 - International Congress on Emergency Medical Service Systems</td>
<td>New Delhi, India</td>
<td>Dr. S. K. Prabhakaran</td>
<td>Tel: +91 26594708, Email: <a href="mailto:info@ems2012.in">info@ems2012.in</a>, URL: <a href="http://www.ems2012.in/">http://www.ems2012.in/</a></td>
</tr>
<tr>
<td>11 – 12 Feb</td>
<td>1st Asia - Pacific Breast Cancer Summit</td>
<td>Singapore</td>
<td>Dr. L. F. Hernisa</td>
<td>Tel: +91 4 311 6300, +65 6496 5500, Email: <a href="mailto:abc2012@mci-group.com">abc2012@mci-group.com</a>, URL: <a href="http://www.abc2012.org/">http://www.abc2012.org/</a></td>
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### MARCH 2012

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<td>3 – 4 Mar</td>
<td>NYSORA Asia 2012</td>
<td>Vietnam</td>
<td>Mr. Yap Hong Yi</td>
<td>Tel: +65 6778 5620, Email: <a href="mailto:na2012@pinghealthcare.com">na2012@pinghealthcare.com</a>, URL: <a href="http://www.NYSORAsia.com/">http://www.NYSORAsia.com/</a></td>
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<td>4 – 7 Mar</td>
<td>EMBO Symposium. Amoebiasis 2012</td>
<td>Khajuraho, India</td>
<td>Dr. N. S. Nagarajan</td>
<td>Tel: +91 0 1147165500, Email: <a href="mailto:amebiasis2012@gmail.com">amebiasis2012@gmail.com</a>, URL: <a href="http://www.indoeb.org">www.indoeb.org</a></td>
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<td>8 – 10 Mar</td>
<td>International Conference on Biologically Active Molecules 2012 (ICBAM 2012)</td>
<td>Dindigul, Tamil Nadu, India</td>
<td>Dr. N. S. Nagarajan</td>
<td>Tel: +91 944202933, Email: <a href="mailto:icbam2012@gmail.com">icbam2012@gmail.com</a>, URL: <a href="http://www.icbam2012.com">www.icbam2012.com</a></td>
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<td>8 – 11 Mar</td>
<td>20th Annual Meeting of the Asian Society for Cardiothoracic Surgery</td>
<td>Bali, Indonesia</td>
<td>Dr. N. S. Nagarajan</td>
<td>Tel: +65 6722 9388, Email: <a href="mailto:enquiry@icpc.com.sg">enquiry@icpc.com.sg</a>, URL: <a href="http://www.healthcareinformaticsasia.com/Event.aspx?id=567330">http://www.healthcareinformaticsasia.com/Event.aspx?id=567330</a></td>
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<td>12 – 13 Mar</td>
<td>2nd Annual International Conference on Advances in Biotechnology (BIOTECH 2012)</td>
<td>Bangkok, Thailand</td>
<td>Dr. N. S. Nagarajan</td>
<td>Tel: +65 6722 9388, Email: <a href="mailto:enquiry@icpc.com.sg">enquiry@icpc.com.sg</a>, URL: <a href="http://www.advbiotech.org">www.advbiotech.org</a></td>
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<td>5th annual BioPharma Asia Convention 2012</td>
<td>Marina Bay Sands, Singapore</td>
<td>Valerie Lim</td>
<td>Tel: +65 6322 2766, Email: <a href="mailto:valerie.lim@terrapinn.com">valerie.lim@terrapinn.com</a>, URL: <a href="http://www.terrapinn.com/exhibition/biopharma-asi">http://www.terrapinn.com/exhibition/biopharma-asi</a></td>
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<td>Marina Bay Sands, Singapore</td>
<td>Valerie Lim</td>
<td>Tel: +65 6322 2766, Email: <a href="mailto:valerie.lim@terrapinn.com">valerie.lim@terrapinn.com</a>, URL: <a href="http://www.terrapinn.com/conference/biologic-manufacturing-world-asia/">http://www.terrapinn.com/conference/biologic-manufacturing-world-asia/</a></td>
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<td>20 – 24 Mar</td>
<td>15th World Conference on Tobacco or Health</td>
<td>Singapore</td>
<td>Lysha Lim</td>
<td>Tel: +61 11 26581061, Email: <a href="mailto:bgupta@textile.iitd.ernet">bgupta@textile.iitd.ernet</a>, URL: <a href="http://www.healthcareindia2012.org.in">http://www.healthcareindia2012.org.in</a></td>
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<td>20 – 23 Feb</td>
<td>Healthcare India 2012</td>
<td>New Delhi, India</td>
<td>Prof. Bhuvanesh Gupta</td>
<td>Tel: +91 11 26591416, Email: <a href="mailto:bgupta@textile.iitd.ernet">bgupta@textile.iitd.ernet</a>, URL: <a href="http://www.healthcareindia2012.org.in">http://www.healthcareindia2012.org.in</a></td>
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<td>22 – 24 Feb</td>
<td>Future of Surgery</td>
<td>Melbourne, Australia</td>
<td>Dr. N. S. Nagarajan</td>
<td>Tel: +65 6722 9388, Email: <a href="mailto:enquiry@icpc.com.sg">enquiry@icpc.com.sg</a>, URL: <a href="http://www.terrapinn.com/conference/biologic-manufacturing-world-asia/">http://www.terrapinn.com/conference/biologic-manufacturing-world-asia/</a></td>
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**Note:** The contact information includes phone numbers, fax numbers, email addresses, and websites for more details about each event. The URLs provided can be used to obtain more information about the events.
April 2012

2 – 4 April
International Conference on Food Science and Nutrition 2012
Kota Kinabalu, Sabah, Malaysia
Tel: +6088 320000
Fax: +6088 320059
E-mail: icfsn2012@ums.edu.my
URL: www.ums.edu.my/conferences/icfsn

12 – 15 April
4th Spring Meeting of the International Society for Dermatologic Surgery (ISDS)
Tel: +1 149 6151 951 8892
Fax: +1 149 6151 951 8893
URL: www.isdsworld.com/en/upcoming-congresses

13 – 15 April
Asian Oncology Summit 2012
Singapore, Singapore
Contact Person: Jason Leng
Tel: +65 6349 0201
Fax: +65 6733 1817
E-mail: j.leng@elsevier.com
URL: http://www.asianoncologysummit.com

13 – 16 April
27th Asia Pacific Academy of Ophthalmology Congress
Busan, South Korea
Email: regi@apaobusan2012.com
URL: http://www.apaobusan2012.com/

20 – 21 April
Organisation for Oncology and Translational Research 8th Annual Conference
Kyoto, Japan
Tel: +11 81 75 761 5717
Email: info@ootr-institute.org
URL: www.ootr-institute.org/conference/8th/

20 – 22 April
The 9th Meeting of Asian Society for Neuro-Oncology (ASNO2012)
Taipei, Taiwan
Contact Person: Xiao Furen
Tel: +886 2 2312 3456 ext 63110
E-mail: admin@asno2012.org
URL: http://www.asno2012.org/

20 – 22 April
ASMMIRT 2012
Sydney, New South Wales, Australia
Contact Person: Lili Lin
Tel: +3 9419 3336
Fax: +3 9416 0783
Email: conferences@air.asn.au
URL: www.air.asn.au/asmmirt2012

25 – 26 April
2nd Annual Biomarkers in Diagnostics & Therapeutics 2012
Singapore
Contact: Ms. Stella Ang
Tel: +65 6853 9156
Email: enquiry@eventprotocol.com

MAY 2012

4 – 6 May
World Congress on Biotechnology
Hyderabad, Andhra Pradesh, India
Contact Person: Hari Krishnan
URL: www.brightice.org

5 – 6 May
2012 2nd International Conference on Chemistry and Chemical Process (ICCCP 2012)
Kuala Lumpur, Malaysia
E-mail: icccp@cbees.org
URL: www.icccp.org/

9 – 11 May
The 4th International Exhibition on BioPharma, Biotechnology & Equipment 2012
Shenzhen, P.R. China
Contact Person: Ms. Mavis Wu
Tel: +852 2827 6766
Fax: +852 2827 6870
Email: general@coastal.com.hk
URL: www.coastal.com.hk/biotech

16 – 19 May
7th World Congress for Neurorehabilitation (WCNR)
Melbourne, Victoria, Australia
Tel: +61 2 9954 4400
Fax: +61 2 9954 0666

19 – 20 May
1st USIM International Conference on Medicine and Health
Kuala Lumpur, Malaysia
Contact Person: Nazefah
URL: http://www.icmh2012.usim.edu.my/website

24 – 25 May
National Medicines Symposium
Sydney, NSW, Australia
Contact Person: Maarinke Van Der Meulen
Tel: +61 2 9384 2133
Fax: +61 2 9384 2133

24 – 27 May
19th WONCA Asia Pacific Regional Conference
Jeju, Korea (South)
Contact Person: Junhee Moon
Tel: +82 2 566 6033
Fax: +82 2 566 6087
E-mail: regi@wonnaicap2012.org
URL: http://www.wonnaicap2012.org

27 – 28 May
17th National Conference on Medical and Health Sciences
Kota Bharu, Kelantan, Malaysia
Contact Person: Abdul Hakim Abdul Basir
Tel: 09 767 5751
Fax: 09 764 2026
Email: cmnhs@kk.usm.my
URL: http://www.dental.usm.my/cmnhs/

27-29 May
ISPE Singapore Conference
Singapore
Contact: Ms Rachel Low
Tel: +65 6780 4671
Email: rachel.low@reedexpo.com.sg
URL: http://www.interphexasia.com/ispe-singaporeconference/

28- 29 May
Interphex Asia 2012
Singapore
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URL: http://www.interphexasia.com/home/
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