Metabolic Syndrome and Diabetes: Current Asian Perspectives

Inflammation and Metabolic Syndrome

Autophagy and its Role in Metabolism
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EDITORIAL

BIOBOARD

AUSTRALIA
5 Mosquito Virus Hits Australia
5 Dairy Intake Could Aid Healthcare Budget
6 New Stem Cells could Fix Broken Hearts

CHINA
6 Toxin Found in Chinese Milk
7 New Way to Detect Liver Cancer Earlier

SINGAPORE
7 TTSH First to Perform Robotic Gastrectomy in SE Asia
8 Doctor Uses Glove Instead of Port in Colon Surgery
8 Singapore & China Scientists Perform Asian Genome-wide study on Kidney Disease

TAIWAN
9 Biologists Generate Man-made Pluripotent Stem Cells to Aid Study of Pompe Disease

SOUTH KOREA
9 Korea’s Medical Policy Improvement Project for Foreign Patients

OTHER REGIONS
10 Single Gene Links Rare Cancers
10 Israeli Scientists Develop Cancer ‘Cluster Bomb’

FEATURES
11 Metabolic Syndrome and Diabetes: Current Asian Perspective
17 Inflammation and Metabolic Syndrome
24 Autophagy and its Role in Metabolism
Upcoming Issues
- February: Antibiotics
- March: Stem Cells
- April: BioEthics

REVIEW
30 Human Cancer Viruses: Past, Present and Future
35 Serpiginous Choroiditis: An Update

INSIDE INDUSTRY
42 CSL Partners US Agency on Key Study to Prevent Common Causes of Abnormalities in Newborns
43 China Sky One Medical to Jointly Launch Adult Stem Cell Research Enterprise
43 China Botanic Announces Development of New Siberian Ginseng Polysaccharide Extract Powder
44 Merck Establishes New MSD R&D Asia Headquarters
44 Nuclear Health, GE Healthcare Join Hands in Fight against Cancer
45 Abbott and Reata Pharmaceuticals Announce Agreement to Develop and Commercialize Next-Generation Antioxidant Inflammation Modulators
46 Lancaster Laboratories Collaborates with BioAzure
46 Samsung and Biogen Idec Announce Joint Venture to Develop, Manufacture and Market Biosimilars
47 Agilent Technologies and Monash University Sunway Campus Boost Talent and Skills for Genomics Research in Malaysia
48 S*BIO's Novel JAK2 Inhibitor Pacritinib (SB1518) Effectively Reduces Splenomegaly in Myelofibrosis (MF) Patients

RESEARCH FINDINGS
49 Study Reveals Link Between Body Temperature and Stillbirth
50 GIS Researchers Develop Systematic Method for Accurate DNA Sequence Reconstruction
51 Taiwan Researchers Find Possible Markers of Stem Cell

CONFERENCE CALENDAR
EDITORIAL

Metabolic Syndrome – The Silent Killer

‘Act on Diabetes. Now’ was the urgent slogan for World Diabetes Day 2011, to raise awareness of diabetes and its prevention. Amongst one of the top four non-communicable diseases listed by the World Health Organization (WHO), almost 366 million people worldwide are estimated to have diabetes and about 4 million died from complications of diabetes, in 2011 alone.

The Metabolic Syndrome (MetS) is a complex disorder comprising a group of interconnected factors, including abdominal obesity, insulin resistance, hypertension and high blood sugar that increase the risk of developing cardiovascular disease and type 2 diabetes mellitus, amongst other chronic metabolic abnormalities. While the underlying cause of MetS continues to challenge the experts, the risk factors of obesity and insulin resistance take centre stage, contributing heavily to the global burden of non-communicable diseases predominantly through diabetes and its sequelae of heart disease and kidney failure. Balancing between energy expenditure and nutrition requirement is a delicate process that can be easily disrupted by environmental and genetic factors leading to the development of MetS. Once considered a disease of the developed West, industrialisation and rapidly accelerating lifestyle changes, in lower and middle income nations across the world have resulted in a dramatic increase in the number of complications, disabilities and mortalities resulting from the metabolic syndrome. Additionally, MetS is evolving in its increasing prevalence in childhood and young adulthood making it a significant concern [1].

Addressing the threat of the Metabolic Syndrome requires a multi-pronged approach to investigate and analyse scientific, clinical, public health and socioeconomic factors. This feature on the metabolic syndrome serves to highlight aspects of current research findings, focusing on cellular aspects of metabolism, abnormalities in insulin signaling, glucose and lipid metabolism that lead to disease, together with an overview of diabetes trends and concerns in Asia. Several mechanisms have been proposed to explain insulin resistance and obesity, one of the more prominent ones being inflammation. Scientific research has progressed to reveal a connection between obesity, inflammation and the metabolic syndrome. These and other important findings are reviewed by Andrew Bressler and Benjamin Bikman. They elaborate on the role of pro-inflammatory factors like Tumour Necrosis Factor alpha (TNFa) and C-reactive protein (CRP) in abdominal obesity, dyslipidemia, hypertension and insulin resistance including the genes and pathways these factors regulate. At the cellular level, interesting observations have revealed a role for autophagy, a cellular survival and recycling strategy, in metabolism and metabolic syndrome. Rohit Sinha summarises the advances and evidences linking autophagy to nutrient sensing and insulin resistance. He reviews the regulation of nutrient sensing metabolic pathways regulated by autophagy and describes genetic findings.
through which autophagy regulates glucose and lipid metabolism in adipose and liver and also importantly, the health of insulin secreting cells in the pancreas. At the population level, epidemiological studies indicate that risk criteria and diagnosis is significantly influenced by ethnicity and economic development. According to the WHO, Southeast Asia and the Western Pacific region are at the forefront of the diabetes epidemic with China and India leading the list of affected countries. Curiously, while childhood obesity is on the rise, several non-obese Asians are insulin resistant suggestive of an epigenetic component [2]. Bodies primed over generations for malnutrition and manual labor are leaving many developing countries in Asia ill-prepared for calorie-dense food and sedentary lifestyles.

While pharmaceutical research has given the world effective drugs to reduce augmentation of the metabolic syndrome, such therapy has its own challenges given the incurable and progressive nature of this syndrome. Costs to families are escalating in terms of healthcare and loss of economic productivity with a high percentage of affected people belonging to the workforce in low and middle income countries. Many patients from such families cannot afford medication and often rural healthcare centres face a shortage of drugs. Additionally, risk groups are not well identified and several thousands of cases go undiagnosed due to the lack of awareness amongst the masses and the lack of access to primary healthcare. The good news is these diseases are largely preventable through lifestyle and dietary changes. The disconcerting news is that governments do not seem to be moving fast enough to tackle this mammoth problem. In the current scenario it is imperative that together with scientific and technological advances, more aggressive and sustainable public health policies are implemented, with a strong emphasis on prevention, whose benefit can be felt by all.

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Sarada Bulchand is a postdoctoral research fellow at Duke-NUS Graduate Medical School, Singapore. She received her Bachelor’s (Hons) in Life Science and Biochemistry from St. Xavier’s College, Mumbai, India. She went on to do her Masters in Molecular Biology from the Tata Institute of Fundamental Research, Mumbai and obtained her Ph.D. in Molecular Biology from Temasek Life Sciences Laboratory, National University of Singapore in 2010, during which she was awarded the Singapore Millennium Foundation Scholarship.

Her research career has been diverse with sprinklings of neurobiology, developmental biology and metabolism in model systems from mice, human cell lines, fruit flies and zebrafish. Her keen interest in ‘bench to bedside’ research brought her to the Program in Cardiovascular and Metabolic Disorders at Duke-NUS. Her current research focuses on the mechanisms of lipid induced insulin resistance and the metabolic syndrome. Besides her scientific pursuits she is also an instructor for a Freshman Seminar module at NUS and enjoys science writing. She is an avid nature lover, bird watcher and musician when time permits!

References:
AUSTRALIA

Mosquito Virus Hits Australia

Australia’s New South Wales (NSW) health authorities issued a warning to residents to take extra precautions to avoid mosquito bites after the detection of mosquito-borne Murray Valley Encephalitis virus (MVE) in the state.

The MVE virus has been detected in sentinel chickens near Leeton, Hay and Moama in southern NSW and in the Macquarie Marshes in the west of the state, NSW Health said. NSW Health Director of Health Protection Jeremy McAnulty said the latest detections should serve as an important reminder for people to protect themselves.

“The important message is to avoid mosquito bites and be alert to any symptoms,” McAnulty said in a statement. “While MVE is relatively rare, and most people will not develop symptoms, it is a serious mosquito-borne disease,” McAnulty said.

“In mild cases, symptoms of MVE include fever, headache, nausea, vomiting and muscle aches. In more severe cases symptoms can include neck stiffness, lethargy, drowsiness, confusion, delirium, tremors, neurological problems and coma in severe cases.” The MVE virus is transmitted by infected mosquitoes which breed in flooded, grassy and swamp areas and around rivers and waterways.

According to NSW Health, the current area of risk for MVE extends in regions west of the Great Dividing Range and people living around rivers and wetlands and in recently flooded areas in western NSW are at the highest risk of catching the mosquito-borne disease.

Dairy Intake Could Aid Healthcare Budget

More than $2 billion dollars could be cut from the nation’s healthcare budget if Australians increased their daily dairy intake, a new UniSA study has found.

According to the researchers, just one in three Australians consumes the recommended daily amount of dairy - two serves for adults, and three serves for teenagers. Lead researcher James Doidge from the university’s Health Economics and Social Policy Group said dairy had beneficial effects against chronic illnesses including obesity, type 2 diabetes, heart disease, stroke, hypertension and osteoporosis.

“It’s been a misconception that calcium is the most or only important thing in dairy,” he said. “But a lot of research coming out lately is showing that there is a benefit tied up with a lot of components in dairy.” It has a whole range of vitamins and minerals and a huge variety of proteins and fatty acids.

Mr Doidge and his team estimated the effects on burden of disease and direct healthcare expenditure if Australians were to increase dairy consumption to recommended levels, finding $2 billion could be saved.

He said 58 per cent of men and 73 per cent of women did not eat two serves of dairy daily, while 62 per cent of boys and 83 per cent of girls failed to meet the higher three-serve recommendation. A serve equals 250ml milk, 40g of cheese or a 200g tub of yoghurt.

Dairy had been wrongly given a bad name because of the high fat content of varieties of cheeses, butter and creams. "Whole fat milk is still a low fat product - it is 96 per cent fat free,” he said. He said the body needed some of the fatty acids found in dairy, while calcium could prevent absorption of fats while also increasing the excretion of fats.
New Stem Cells could Fix Broken Hearts

A rare type of stem cell could hold the key to mending a broken heart. Australian scientists have discovered a new type of stem cell in mouse hearts which they believe plays a vital role in maintaining the muscle and its vessels.

They hope the cells could one day be used to regenerate and repair the literally broken hearts of people who have suffered a heart attack or heart disease. The scientists from the Victor Chang Cardiac Research Institute in Sydney and University of NSW made the discovery during a seven-year study of heart stem cells in mice.

Lead researcher professor Richard Harvey said it appeared the heart stem cells’ main role was to replace damaged vessels. “In an injury situation where many of the vessels are killed and great slabs of tissue die, like in a heart attack, you need to replace muscle and vessels,” he said. “We think these cells are intimately involved in the regeneration of the heart and replacement of the old heart tissue as the organism ages.”

Heart disease is the leading cause of death in Australia, accounting for 16 per cent of all deaths in 2009. Drugs used to treat the disease and heart attacks aim to protect the muscle from working too hard. But stem cell therapies offer the potential to regenerate damaged or diseased heart muscle and tissue. Separate research carried out in the United States recently found when bone marrow stem cells were injected into adults they successfully replaced damaged heart muscle and got it to pump better.

Prof Harvey said the heart stem cells discovered in Australia had the potential to provide even better results. The newly-discovered cells work in a similar fashion to bone marrow stem cells – which help repair damaged tissue in several different organs – but are specifically dedicated to keeping the heart healthy. Prof Harvey believed the heart cells could one day be combined with other stem cells in a new type of regeneration therapy to treat damaged hearts.

Currently, stem cells are mainly used after being extracted from the body and grown in a laboratory before they are injected back into a patient to repair a damaged or diseased organ.

However, Prof Harvey said the discoveries about how the heart stem cells work could help scientists determine the best way to stimulate them in the body so they could race directly to damaged areas and repair them.

The Australian researchers plan to carry out more studies to see if human hearts contain the same type of stem cells found in mice. If so, they plan to test the cells in animals before carrying out clinical trials with heart patients.

CHINA

Toxin Found in Chinese Milk

China has discovered excessive levels of a cancer-causing toxin in milk produced by one of the nation’s leading dairy companies, the firm said, in the latest in a series of food safety breaches.

The government’s quality watchdog found high levels of an aflatoxin, which is caused by mould, in milk produced by the Mengniu Dairy Group, the company said in a statement issued recently. Mengniu said the milk, produced at one of its plants in the southwestern province of Sichuan, was tested before being sold so the contaminated milk never reached the market.

China is trying to crack down on product safety violations to reassure citizens and restore faith in the government after a series of high-profile scandals. Milk was at the centre of China’s biggest food safety scandal in 2008 when the industrial chemical melamine was found to have been illegally added to dairy products to give the appearance of higher protein content.

At least six babies died and another 300,000 became ill after drinking milk tainted with melamine. Product safety problems have been found in goods ranging from pharmaceuticals to cooking oil. In September, the government arrested 32 people over the sale of cooking oil made from leftovers taken from gutters.

Aflatoxins can be found in milk after cows consume feed contaminated by mould and can increase the risk of cancer, including liver cancer, according to the World Health Organisation. Mengniu said the products had been destroyed, and apologised to consumers. The General Administration of Quality Supervision, Inspection and Quarantine made the latest discovery in nationwide testing of 200 dairy products made by 128 companies, the agency said separately.
New Way to Detect Liver Cancer Earlier

A simple test using just one milliliter of a patient’s blood can tell whether the patient has liver cancer — even if the tumor is less than two centimeters in diameter, new medical research in Shanghai shows.

Doctors at the Zhongshan Hospital, a major medical institution affiliated with Fudan University, have found that seven microRNAs, or ribonucleic acid molecules, are strongly related to liver problems. This discovery can raise the accuracy of tests for early-stage liver cancer to almost 90 percent.

Each test will cost a patient only about 100 yuan ($15.9), said Dr. Fan Jia, vice president of the hospital and one of the country’s leading liver surgeons.

The research results have been published on the website of the Journal of Clinical Oncology, the official journal of the American Society of Clinical Oncology.

China sees half of the world’s new liver cancer cases each year. More than 60 percent of Chinese liver cancer patients are diagnosed too late to be cured, according to the medical paper written by Fan’s team.

Fan said that the current check for liver cancer, which is based on the volume of alpha-fetoprotein (AFP) in blood, was not accurate for some people, including pregnant women and patients with hepatitis, gonadal carcinoma or gastrointestinal cancer, as their AFP levels are also possibly high.

Fan’s team examined blood samples from 934 people, including healthy people and those with hepatitis B, cirrhosis or liver cancer between 2008 and 2010. The team found that seven of the more than 130 microRNAs in their blood were closely linked to liver problems, and could, therefore, be used to test the health of a person’s liver.

The team is applying for patents for the test in China, the United States, Japan and the European Union, and is still in the process of developing a microchip containing the seven microRNAs before the test will be adopted on a large scale.

SINGAPORE
TTSH First to Perform Robotic Gastrectomy in SE Asia

A more precise surgery method is now available to those suffering from stomach cancer. Tan Tock Seng Hospital (TTSH) has become the first in Southeast Asia to perform the robotic gastrectomy procedure.

Stomach cancer is the fifth most common cancer in Singapore, and doctors say that stomach cancer is largely triggered by poor lifestyle choices, such as overeating or eating too much barbequed food. Only a small percentage is caused by genetic factors.

75-year-old Loh Ah Mye was diagnosed with stage one stomach cancer last month. But due to her age, doctors found it risky for her to go through the usual key hole surgery to remove cancer cells.

She opted to undergo the robotic gastrectomy procedure, and became the first person in Southeast Asia to do so. The procedure is commonly performed in Korea and Japan, where the incidence of stomach cancer is high. Madam Loh said: “I really did recover quite quickly. When I woke up from the operation, yes I was in pain, but I could get up to walk around and also go to the toilet.”

The surgeon performing the robotic gastrectomy procedure operates on the patient through the use of a console while watching a 3D high-definition screen. Instruments, which are mounted on robotic arms controlled by the doctor, are then inserted into the body.

The robotic arms are able to mimic the movement of the hand and the wrist within the abdomen. This allows freer movement and precision. This especially helps lymph node dissection, which is much more difficult to perform in laparoscopic surgery.

The portion affected by cancer cells in the abdomen is then removed.

The surgery is typically conducted on people with stage 1 and 2 cancer, when the affected area is still relatively small. Trials are underway to see if such a surgery is suitable for later stages of stomach cancer.

Dr Jaideepraj Rao, a consultant with the Department of General Surgery at TTSH, said: “In this kind of key hole surgery or robotic surgery, the incisions are extremely small, so the pain is much less and they recover faster. We have high-definition cameras that can zoom in, so really we see the field magnified, every small structure can be identified, so our dissection is very meticulous and there’s less blood loss.”

Madam Loh said she still suffers from some side-effects from the operation, as she still throws up some of her food.

But doctors said that this is a common response to most stomach surgeries.

Currently the robotic gastrectomy method costs more for the patient.

However, doctors said the price is likely to drop, as they expect more people to opt for this kind of surgery. This method has also been used in other hospitals in Singapore for prostate and colon cancer.
Doctor Uses Glove Instead of Port in Colon Surgery

A surgeon from Tan Tock Seng Hospital has become the first in Singapore to perform a new colon re-sectioning surgery using a common glove. The Single Incision Laparoscopic Surgery, or SILS for short, usually involves an expensive equipment costing up to $2,000. With SILS, a small incision of about 4cm is made to reach the colon with robotic arms. But the robotic arms need a port - which is expensive - to fit the needles for the surgery.

However, Dr Leong Quor Meng, a consultant of general surgery, learnt from South Korean doctors a technique to replace the mechanical port with a glove. And it works just as well. He said he picked up the technique during his overseas training in Korea to learn robotic surgery last year. He noticed that surgeons used a non-powdered glove, which costs only around a dollar, amongst other cheaper equipment.

By using a glove, equipment cost for SILS is cut by nearly 90 percent to just S$65. Dr Leong said the technique can be useful if the tumour isn’t large. And he is confident one third of his patients can benefit from the approach of using gloves as modified "ports" and emerge with minimal scarring.

He said: “The advantages of this surgery are that it is cheap, the ports are cheap, and the outcome is very good. The patients recover fast, the cosmesis is excellent and we can provide it to all patients.”

Singapore & China Scientists Perform Asian Genome-wide study on Kidney Disease

Singapore and China scientists perform large Asian genome-wide association study on kidney disease

Singapore and China scientists, headed by Dr Liu Jianjun, Senior Group Leader and Associate Director of Human Genetics at the Genome Institute of Singapore (GIS) and Dr Yu Xueqing, a nephrologist at the 1st Affiliated Hospital of the Sun Yat-Sen University, have identified new susceptibility genes for the kidney disease Immunoglobulin A Nephropathy (IgAN). This discovery, reported in the advance online issue of Nature Genetics on 25 December 2011, brings scientists closer to understanding the disease and working towards its cure.

IgAN is a kidney disease characterized by the deposit of IgA in the mesangial area of glomeruli. Disease prevalence among Asians is as high as 3.7%, less common in Caucasian population (up to 1.3%) and very rare among individuals of African ancestry. It is the most common cause of kidney failure among Asian populations, 15-40% of the patients end up on dialysis or require kidney transplants. The pathogenesis of IgAN is not clear, but both genetic and environmental factors likely contribute to its development.

In order to identify susceptibility genes for IgAN, Drs Liu and Yu and their collaborators carried out a large genome-wide association study of IgAN in Chinese Han population. First, they performed a comprehensive genome-wide analysis of common genetic variants in 1434 patients and 4270 controls. Subsequently, they investigated 61 regions of human genome for a validation study in 2703 patients and 3464 controls. The researchers discovered two novel susceptibility genes, TNFSF13 on 17p13 and DEFA on 8p23 as well as several HLA alleles and haplotypes within MHC region that are associated with IgAN development. They further found that the risk variants within MHC could also influence the clinical symptoms of IgAN patients. The newly discovered susceptibility loci implicate the genes related to innate immunity and inflammation, suggesting their important role in the development of IgAN. Their study also confirmed the previously reported susceptibility locus on 22q12 in Chinese and European populations.

Dr Liu said: “The discovery of the new disease susceptibility loci is a major breakthrough of IgAN research. It is interesting to see that some genetic variants can influence both susceptibility and clinical presentation of the disease.” Dr Yu added: “These findings offer us opportunities to identify important biological pathways involved in IgAN development and further explore novel approaches to intervene and thus prevent affected patients from developing severe kidney damage.”

The GIS is a research institute under the umbrella of the Agency for Science, Technology and Research
Biologists Generate Man-made Pluripotent Stem Cells to Aid Study of Pompe Disease

Assistant Research Scientist at the Stem Cell Program of Institute of Cellular and Organismic Biology/Genomics Research Center, Dr. Hung-Chih Kuo and his colleagues recently successfully generated the world’s first Pompe disease-specific induced pluripotent stem cells. These stem cells constitute a promising model through which to test drugs and disease markers for Pompe disease.

Pompe disease (also known as glycogen storage disease type II) is a genetically inherited disorder caused by mutations in the gene encoding the enzyme acid alpha glucosidase (GAA). Without treatment, most patients with the infantile-onset form of Pompe disease die by the age of 18 months. Current understanding of the progression of Pompe disease during development is still limited, partly due to the difficulty in obtaining proper cell specimens from patients. To develop efficient therapies, researchers need to discover ways to obtain a more thorough understanding of the development of Pompe disease at the cellular level.

Pluripotent stem cells are unique among the different types of cells found in the body in that they are able to differentiate into a myriad of other types of cells, a characteristic known as “pluripotency”. So called “induced pluripotent stem cells” (iPSCs) are man-made pluripotent stem cells that can be generated from any individual, including individuals with sporadic and inherited genetic diseases. These cells resemble human embryonic stem cells in many aspects. However, the generation of iPSCs from disease cells (such as those found in the infantile form of Pompe disease) is challenging, as reprogramming efficiency may be compromised by defects caused by the diseased nature of the cells.

Dr. Kuo and his colleagues generated iPSCs specific to Pompe disease and showed that these cells possess human embryonic stem cell characteristics and pluripotent developmental propensity. Furthermore, they demonstrated that these Pompe disease iPSCs are able to give rise to cardiomyocytes, a type of specialized cell found in heart muscle) which exhibited the characteristics of Pompe disease. Drug rescue assessment revealed that the diseased cardiomyocytes could be rescued by various drug treatments including rhGAA, L-carnitine, and 3-MA. In addition, marker genes whose expression robustly correlated with the therapeutic effect of the drug treatment were identified.

The research was published in the advance access online edition of the journal Human Molecular Genetics on September 28. The full-text of the study entitled “Human Pompe disease-induced pluripotent stem cells for pathogenesis modeling, drug testing and disease marker identification” is available at the Human Molecular Genetics journal website at: http://hmg.oxfordjournals.org/content/early/2011/09/28/hmg.ddr424.full

Korea’s Medical Policy Improvement Project for Foreign Patients

The Ministry of Health and Welfare (Minister Rim Chemin) and the Korea Health Industry Development Institute (President Ko Kyung-hwa) launched a project to improve the medical service system for foreign patients by designating 38 tasks, including seven major issues such as adopting a compensation system for medical injuries and granting permission for drug dispensing in hospitals, to minimize inconveniences for foreign medical patients.

In particular, Korea’s seven major tasks for foreign patients include adopting a compensation system for medical injuries; easing floor area ratio regulations for the building and remodeling of lodging facilities in medical institutions; allowing drug dispensing in hospitals; expanding training programs at the Medical Korea Academy and permissions granted to foreign medical professionals to participate in clinical studies; increasing the cultivation of professional medical workforces; assessing foreign patient accommodation in each medical institution; and improving the visa system.

Korea is considering establishing a credit union for hospitals that treat foreign patients and providing partial support for the funds with government subsidies. Medical Korea is reviewing the plan to ease floor area ratio regulations when medical institutions build or remodel lodging facilities in hospitals for foreign medical tourists and provide them with financial support or loans through a tourism promotion fund.

In addition, Korea is seeking to offer one-stop medical services to foreign patients by allowing hospitals to dispense drugs for foreigners so that foreign patients do not have to suffer inconveniences resulting from the separation of drug prescription and dispensing. Korea is also planning to expand training programs for foreign doctors and actively cultivate professional medical workforces, such as medical interpreters.

An official with the Korea Health Industry Development Institute expects that improvements in medical policies for foreign patients will contribute to the establishment of Korean medical infrastructure with world-class services, on the one hand, and allow Medical Korea to lay the foundation for Korea to take a leap forward with global competitiveness in Asia.
OTHER REGIONS

Single Gene Links Rare Cancers

Canadian researchers have discovered that a common gene links a number of rare reproductive cancers, a finding that could lead to new approaches for treatment.

Ovarian, uterine and testicular cancer were all found to have the same mutation in a gene called DICER, said the research in the New England Journal of Medicine. Scientists have known about DICER for many years, but its exact role in sparking tumour cells to grow has been unclear.

When the gene mutates, DICER’s function is changed “so that it participates directly in the initiation of cancer, but not in a typical ‘on-off’ fashion,” said co-author Gregg Morin, a lead scientist from the Michael Smith Genome Sciences Centre at the British Columbia Cancer Agency.

“DICER can be viewed as the conductor for an orchestra of functions critical for the development and behavior of normal cells,” explained co-author Gregg Morin, a lead scientist from the Michael Smith Genome Sciences Centre at the British Columbia Cancer Agency.

“The mutations we discovered do not totally destroy the function of DICER, rather they warp it - the orchestra is still there but the conductor is drunk.” Researchers are examining whether DICER plays a role in other cancers, and will investigate if mutant DICER can be manipulated to treat the cancers it causes.

Ovarian cancer kills about 15,000 women in the United States each year, and about 22,000 new cases are diagnosed annually. More than 46,000 cases of uterine cancer and 8,100 deaths arise each year in the United States. Testicular cancer is more rare, with 8,300 new cases per year and 350 US deaths, according to the American Cancer Society.

“Huntsman, Morin and colleague’s very exciting discovery of specific mutations in DICER, a factor essential for syntheses of small regulatory RNAs in ovarian and other human tumors, could lead to new approaches to treatment.”

Israeli Scientists Develop Cancer ‘Cluster Bomb’

Israeli medical researchers say they have developed a new technique for blasting cancer tumours from inside out which reduces the risk of the disease returning after treatment.

Tel Aviv University professors Yona Keisari and Itzhak Kelson are about to start clinical trials of a pin-sized radioactive implant that beams short-range alpha radiation from within the tumour.

Unlike conventional radiation therapy, which bombards the body with gamma rays from outside, the alpha particles “diffuse inside the tumour, spreading further and further before disintegrating,” a university statement quoted Keisari as saying. “It’s like a cluster bomb — instead of detonating at one point, the atoms continuously disperse and emit alpha particles at increasing distances.”

The university said that the process takes about 10 days and leaves behind only non-radioactive and non-toxic amounts of lead. “Not only are cancerous cells more reliably destroyed, but in the majority of cases the body develops immunity against the return of the tumour,” the statement said.

The wire implant, inserted into the tumour by hypodermic needle, “decays harmlessly in the body,” it added. It went on to say that in pre-clinical trials on mice, one group had tumours removed surgically while another was treated with the radioactive wire.

“When cells from the tumour were reinjected into the subject, 100 percent of those treated surgically redeveloped their tumour, compared to only 50 percent of those treated with the radioactive wire,” it said. “The researchers have had excellent results with many types of cancer models, including lung, pancreatic, colon, breast, and brain tumours.” It added that the procedure would begin clinical trials at Beilinson hospital, near Tel Aviv, “soon.”
The human body derives energy from food through metabolism. These life sustaining chemical reactions are designed to regulate and respond to energy requirements and the nutritional status of the body. When the body is in a starved state, lipids from adipose tissue are utilised as the energy source mainly in muscle and the heart, while glucose from the liver functions to regulate the central nervous system. The fed state induces a systemic hormonal response particularly the secretion of insulin in response to glucose in the blood. Insulin, the primary regulator of blood glucose levels and a major anabolic hormone, is secreted by the beta cells of the pancreas, regulating the uptake of glucose into peripheral tissues, mainly muscle and adipose while suppressing glucose output from the liver. This serves to provide glucose as a source of energy to all cells while also maintaining blood glucose levels within acceptable limits. Homeostasis of plasma glucose levels is critical to normal body function wherein both hyper (excess) and hypoglycaemia (low levels of plasma glucose) are severely detrimental to health.

Metabolic Syndrome (MetS), originally called Syndrome X or insulin resistance syndrome, is a cluster of factors that increase the risk of cardiovascular diseases and Type 2 diabetes mellitus (T2DM). While there have been frequent modifications to the definition, the main components of the syndrome are insulin resistance, abdominal obesity (as well as lipid deposition in other non-adipose sites) with particular emphasis on waist measurement, glucose intolerance/hyperglycemia, dyslipidemia (especially low High Density Lipoprotein (HDL) cholesterol, increased triglycerides, and apolipoprotein B levels) and hypertension[1]. Epidemiological studies have revealed that the prevalence of MetS is influenced greatly by factors like sex, age, race and ethnicity in addition to the defined criteria. Data strongly suggests that metabolic syndrome is often an immediate precursor of Type 2 diabetes and cardiovascular disease with central obesity and insulin resistance amongst the primary risk factors [2].

Diabetes Mellitus is a group of common metabolic disorders that share the phenotypes of hyperglycemia characterised by decreased glucose utilisation due to insulin resistance, increased glucose production from the liver and decreased insulin secretion from the pancreas. It is classified on the basis of aetiology and clinical presentation into four types of which Type 2 diabetes (T2DM) is the focus of this article. T2DM is characterised by reduced sensitivity of target tissues to insulin action (insulin resistance). Later stages include relative insulin deficiency due to pancreatic beta cell loss as these cells go into overdrive to produce more insulin to cope with high blood glucose levels. T2DM constitutes 90-95% of all cases of diabetes and is often associated with obesity, which itself can cause insulin resistance and lead to elevated blood glucose levels [3]. Highlights of epidemiological trends, risk factors, mechanisms, socioeconomic concerns, prevention and public health policy are discussed in subsequent sections.

The consequences of chronic elevation in blood glucose levels, even when no symptoms are present to alert the individual of diabetes,
lead to tissue damage. Uncontrolled diabetes can be fatal due to various complications. When blood glucose is poorly controlled over long periods, blood vessels in multiple tissues throughout the body undergo abnormal structural and functional changes resulting in decreased vascular supply to various organs and tissues. This in turn leads to an increased risk for heart-attack, stroke, end stage renal disease, retinopathy (damage to the retina) and blindness and nerve damage commonly in the feet and legs, leading to major infections and amputations. The inability to use glucose for energy needs leads to increased utilisation of stored proteins and fats eventually resulting in severe wasting of tissues and death. Fasting blood glucose levels > 126mg/dL and impaired glucose tolerance are commonly used diagnostic criteria for diabetes. Levels of glycated haemoglobin (HbA1C) are used to assess the condition over a longer period especially when patients are being treated with anti-diabetics [2, 3]. The risk factors and consequences are diabetes are summarised in Figure 1.

**Type 2 Diabetes** once prevalent largely in affluent Western countries is now a global health priority with developing nations being hit the hardest. In the last decade, diabetes has emerged as a major public health and socioeconomic burden in Asia and Asia-Pacific. The Asian diabetes paradox reveals a mismatch between affluence and diabetes prevalence. The International Diabetes Federation has predicted that the number of individuals with diabetes will increase from 366 million in 2010 to 551 million in 2025 with 80% of the disease burden in low and middle-income countries [2]. More than 60% of the world population with diabetes will come from Asia and deaths due to diabetes will double between 2005-2025. While China and India top the world list (Figure 2), the other heavily populated nations of Bangladesh, Indonesia, Pakistan, Philippines and Thailand are amongst the top 20 countries in the world for the number of diabetes cases. In addition to the number of people with frank diabetes, the prevalence of impaired glucose tolerance is high in many Asian countries suggesting the presence of a large pool of people with the potential to develop diabetes. The rapidly increasing rate of diabetes in Asia is associated with a strong interaction between genes and the environment propelled by accelerated lifestyle changes and modernisation. While overall criteria, definitions and risk factors are similar across the world, a wealth of information indicates that heterogeneity in ethnicity, cultures, stages of socio economic development and local public health policies affect clinical presentation, management and prevention of diabetes [2, 4-6].

**The Obesity Epidemic:** Numerous studies in animal models and population studies in human patients have repeatedly shown that there is a strong correlation between obesity, insulin resistance, diabetes and its complications. Asia has undergone a tremendous change in demography and lifestyles with greater movement in populations from rural to urban areas, improved socioeconomic conditions, change in diets with higher intake of cheap calorie dense foods high in saturated fat, like palm oil and high fructose corn syrup (HFCS) in sweetened beverages [7, 8]. The greater availability of processed foods both eastern (instant noodles) and western (burgers and fries) together with sedentary lifestyles has resulted in over-consumption and an expansion of waistlines. The rate of increase...
in obesity in Asia has been far more rapid compared to other parts of the world. Asian populations especially those of South Asian descent are more prone to abdominal obesity with increased insulin resistance compared to their Western counterparts. Thus, waist circumference reflecting central obesity is a useful measure of obesity-related risk of T2DM especially in individuals with normal BMI values. Using imaging technologies like computed tomography (CT scans) to measure total body fat and specific fat depots it was observed that healthy Chinese and South Asian individuals had a greater amount of visceral obesity than Europeans with the same BMI or waist circumference. This and other studies suggest that Asians seem predisposed towards developing abdominal obesity [2, 4, 6, 9]. In Singapore alone, the obesity prevalence which stood at 5% in 1984 was 10.2% in 2010 and prevalence of T2DM was 11% in 2011[9]. The increasing trend of childhood obesity in Asia, due to overnutrition and underexertion places many young individuals at risk for T2DM in early adulthood. Once considered a disease of the elderly, T2DM is disproportionately high in young to middle aged adults in countries like India and China not just due to obesity but also due to increased stress, depression, shorter sleeping hours and higher rates of smoking all of which are associated with changing lifestyles. In a meta-analysis study, depression was associated with a 60% increased risk of T2DM while smoking was associated with a 44% increased risk of developing T2DM indicative of psychosocial risk factors [4, 6]. It has been shown that structured diet and exercise have clear benefits by reducing visceral fat and increasing insulin sensitivity [10, 11].

Developmental and Epigenetic Factors: Increased insulin resistance that is not accounted for entirely by fat distribution or obesity has led researchers to investigate evolutionary and genetic differences viz., the ‘thrifty gene’ hypothesis. Intrauterine and postnatal environments can affect the future risk of diabetes via epigenetic fetal programming. Conditions like low birth weight and exposure to undernutrition in utero are common in countries like India where 30% of infants are underweight. These infants are subsequently exposed to calorie rich diets which their genomes have not been programmed for. The mismatch between metabolic phenotype that was programmed during fetal growth and the nutritionally rich postnatal environment puts the infant at increased risk for obesity, insulin resistance and diabetes. A study in India showed that underweight in infancy and overweight at 12 years of age was associated with increased risk of developing impaired glucose tolerance or diabetes in young adulthood. Additionally, offspring of women who are obese, have T2DM or have had gestational diabetes during pregnancy are at increased risk of developing diabetes themselves due to several reasons like genetic predisposition, familial lifestyles and in utero exposure to increased levels of insulin which promotes excessive growth in the fetus. In the view of increasing childhood obesity and increasing number of young women with diabetes in Asia, this is likely to create of viscous cycle of diabetes begetting diabetes [4, 6, 9].

Genetic Factors: Diabetes does run in families, suggestive of a strong genetic component. But teasing apart the causative genes is challenging due to the polygenic nature of T2DM. Although, prior to the age of genome wide surveys, using the candidate variant or gene approach, data from multiple

Figure 2. Comparison of estimated diabetes cases (in millions) in major Asian nations in 2011 and predicted number of cases in 2030. Adapted from the Diabetes Atlas, 5th Ed, International Diabetes Federation.
PPAR studies identified two genes that act as targets for widely used anti-diabetic drugs, PPARγ (Peroxisome proliferator-activated receptor gamma) and KCNJ11 (potassium inwardly-rectifying channel, subfamily J, member 11) [12]. In a recent milestone in 2011, a genome wide association study amongst people originating from South Asia (India, Pakistan, Sri Lanka and Bangladesh) identified six new genetic variants linked to type 2 diabetes in these populations[13]. These findings give important new insight into genetic predisposition to diabetes in this population, which in the long term might lead to new treatments. Further identification of DNA variants across populations will, it is hoped, provide clues to the processes involved in the pathogenesis of obesity and diabetes. Given the multi-faceted nature of T2DM, it would not be surprising if each patient has an individual 'barcode' of susceptibility alleles and protective alleles across many loci. For example, Pro 12 Ala polymorphism of the PPARγ gene which affords protection against diabetes and insulin resistance to Caucasians, does not appear to protect Indians [12]. Therefore, it is important to study the same problem in different ethnic groups and such genetic data would be most useful if integrated with clinical and biochemical data.

Mechanisms: Given the complexity of type 2 diabetes at the cellular and molecular levels it is critical to understand the pathways that contribute to this dysfunction of multiple organ systems through basic and clinical research. This would serve dual purposes of deciphering diabetes at a mechanistic level and opening the doors to potential preventive and therapeutic measures. Obesity and insulin resistance at the cellular level involve a host of molecular and biochemical factors all of which are under intense investigation and most of which are not completely understood. Toxic lipid metabolites deposited in tissues not suited to store lipids, like liver and muscle have been strongly implicated in the development of insulin resistance. Saturated fats from the diet are metabolised into these toxic species that inhibit insulin signalling [14–16]. Another dietary factor that has more recently been shown to disrupt insulin sensitivity, also possibly through lipid deposition, is fructose in the form of high fructose corn syrup present in processed foods and juices. These calorie dense, low fibre diets have influenced the progression of diabetes in Asia. Research has also focused on events leading to loss of function and mass of pancreatic beta cells. While lipotoxicity and glucolipotoxicity are popular theories, the exact cause of this loss is not known [17, 18]. Several studies have also focused on the role of lipids in oxidative stress and mitochondrial dysfunction [19].

Metabolomics: Mechanisms of disease are unravelled also through technological advances that help uncover mechanisms of disease while simultaneously serving as platforms for the discovery of biomarkers and novel therapeutic strategies. Genome wide association studies and mRNA profiling have revealed significant amounts of information but are relatively mature technologies. The analysis of metabolites through metabolomics is a relatively newer and powerful approach to study diabetes both at the systems and molecular levels. Metabolomics measures biological chemicals that result from genomic, transcriptomic and proteomic variability thus providing an integrated profile of biological status for comparisons in health and disease. Duke-National University of Singapore Graduate Medical School is on its way to housing a metabolomics facility with the vision of understanding fundamental mechanisms of metabolic disorders like MetS and diabetes.

One of the major metabolomic platforms is mass spectrometry. Given the role of lipids in diabetes and MetS and the increasing number of patients with these disorders, a detailed analysis of cellular lipids is highly valuable. While it is easier to study proteins and carbohydrates, lipidomics is fairly challenging due to the immense structural and molecular diversity of lipids—in the hundreds of thousands according to some estimates— and also the highly specialised technology required to extract, purify, separate and analyse lipids. But plasma, tissue, cell and even organelle lipidomic studies have the potential to identify new avenues of research and improve quantification of disease risk amongst other advantages [20, 21].

Public Health Policy: Tackling the growing twin epidemics of obesity and diabetes is no small challenge. At the recently held UK-Singapore diabetes and obesity symposium, 2011, engaging discussions highlighted pertinent socioeconomic and public health concerns. These disorders result in the loss of economic productivity due to premature mortality and increasing disabilities which may be more than the direct medical cost incurred especially in low income households in countries like China and India. The lack of subsidised healthcare makes the problem more severe. In countries like India, Sri Lanka and Malaysia there is a lack of good quality public hospitals and lack of drug supplies. There is a flourishing private hospital sector which is curative but not preventive, coupled with a severe lack of primary healthcare especially in low income areas. Additionally, screening and identification of risk groups is weak. Countries like China, South Korea, Taiwan, Philippines and Vietnam have marginally better healthcare but it is also curative [9]. The importance and relevance of ‘prevention is better than cure’ cannot be overstated in the current scenario. There is a need for a greater concerted effort towards prevention of obesity and diabetes through better and more effective public health policies that do not simply remain on paper but are implemented and sustained on the ground. While some countries are beginning to consider changes in their healthcare policies, others like Singapore are already implementing practical measures to reduce incidences of diabetes for example by collaborating with hawker centres to provide people with healthier food options [9, 22]. Clearly these twin epidemics are not just a scientific and medical problem but that which also needs to be addressed by the sectors of law, agriculture and the food industry, business, advertising and education. Making exercise an interesting routine, education of the masses and implementation of measures that make the food industry more accountable are some preventive strategies that could be considered. As fundamental and clinical research advances towards understanding mechanisms of diabetes and obesity, more effective primary healthcare and public policy measures could help reduce this growing threat in Asia.
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Her research career has been diverse with sprinklings of neurobiology, developmental biology and metabolism in model systems from mice, human cell lines, fruit flies and zebrafish. Her keen interest in ‘bench to bedside’ research brought her to the Program in Cardiovascular and Metabolic Disorders at Duke-NUS. Her current research focuses on the mechanisms of lipid induced insulin resistance and the metabolic syndrome. Besides her scientific pursuits, she is also an instructor for a Freshman Seminar module at NUS and enjoys science writing. She is an avid nature lover, bird watcher and musician when time permits!
Inflammation and Metabolic Syndrome

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Sangye Gyamtso, a seventeenth century Tibetan scholar, noted that, “overeating ... causes illness and shortens lifespan”. Thus, without even an understanding of a biochemical pathway, early scholars recognized excess weight as harmful to health. Indeed, obesity predisposes individuals to a host of health complications, including insulin resistance, hypertension, and dyslipidemia, which collectively constitute the metabolic syndrome. Due to the massive and sustained increase in obesity and the prevalence of the metabolic syndrome worldwide, extensive efforts have been devoted to better understand the cellular events that mediate these pathologies.

Inflammation and Metabolic Syndrome

The term inflammation as used in the context of obesity and metabolism is applied to explain the phenomenon of higher levels of circulating pro-inflammatory factors (e.g. C-reactive protein (CRP), TNFα, Interleukin-1β (IL-1β), etc.) with fat mass expansion, rather than an actual redness and swelling of a particular area resulting from infection. Hotamisligil et al. were the first to discover the molecular link between obesity and inflammation when they identified adipose tissue as a site of proinflammatory cytokine synthesis and excretion. Since that time, scientists have found inflammation to be connected with all aspects of the metabolic syndrome. Various definitions exist that identify the metabolic syndrome, though essentially all include central obesity, dyslipidemia, hypertension, glucose intolerance, and insulin resistance. While the constellation of problems may seem somewhat benign, the consequences are very real—those with the syndrome have roughly four times the risk of dying from cardiovascular complications and have double the risk of all-cause mortality. As such, efforts have focused on understanding the etiology with particular attention on the molecular mechanisms that lead to disease onset. A milestone was reached when it was discovered that obesity is associated with a chronic inflammatory state that exacerbates several prominent diseases, including all facets of the metabolic syndrome. In fact, elevated circulating CRP levels are so consistently correlated with the metabolic syndrome that some have recommended the inclusion of a proinflammatory state as one of the syndrome’s components.

Central Obesity

While most discussions with obesity and inflammation assume the perspective of obesity causing inflammation due to adipose–released cytokines, there is an undercurrent of thinking that inflammation may exacerbate obesity. Cani et al. found that mice receiving a continuous infusion of bacterial lipopolysaccharide (LPS), a proinflammatory innate immune response activator, experienced similar weight gain as littermates fed a high-fat diet. This might explain why mice lacking a functional LPS response (CD14 or TLR4 mutant mice) are protected from diet-induced obesity.

Interestingly, LPS-induced weight gain occurs without an increase in energy intake, indicating that dietary fat content is not sufficient to explain obesity. A possible link is the unexpected role of gut bacteria in regulating host energy homeostasis. Obesity is considered by some to be an inflammatory disease, where changes in gut bacterial content and function are considered mediating elements driving adiposity and metabolic disturbances. Not only does high-fat diet increase LPS absorption from the gut, which has been shown exacerbate obesity, but substances known to nourish non-LPS-containing bacteria, known as prebiotics, have been shown to actually reduce adiposity. These and similar efforts have been beneficial in helping the scientific community identify means to treat metabolic problems. Kim et al. suggest directing treatment towards inflammation via a dual approach consisting of pharmacological and dietary methods. For example, nutraceuticals can be used as a safe therapeutic means to combat insulin resistance. Exercise has also been shown to be an important therapeutic method. Teixeira et al. found that the proinflammatory cytokines, IL-6 and TNFα, as well as hyperuricemia all decreased in response to exercise, leading...
them to conclude that exercise is “anti-inflammatory in nature”, although whether this anti-inflammatory effect is necessary for exercise-induced weight loss is unknown.

**Dyslipidemia**

Inflammation leads to harmful changes in lipid metabolism. Dyslipidemia refers to an abnormal amount of lipid in the blood. Much of the evidence linking inflammation to dyslipidemia revolves around the TNFα, the prototypical pro-inflammatory molecule. A host of correlational evidence exists, wherein patients with dyslipidemia also exhibit elevated plasma TNFα levels and interventions that improve lipid profile correlate with reduced plasma TNFα. In fact, the correlation is so consistently observed that some suggest TNFα be used as a marker for familial combined hyperlipidemia. Further, TNFα treatment in mice elicits an acute increase in plasma triglyceride and prolonged administration of recombinant human TNFα reduces beneficial HDL cholesterol.

One mechanism that explains TNFα’s impact on dyslipidemia is via free fatty acid (FFA) production. In general, three sources of FFA are thought to exist: i) dietary FFA, ii) TAG lipolysis, and iii) de novo FFA synthesis; TNFα has been shown to impact lipolysis and de novo FFA synthesis. TNFα administration has been shown to activate adipocyte lipolysis, greatly increasing circulating FFA and TAG. Scratching beneath the surface, Sethi et al. found that the lipolytic effects of TNFα required TNFα receptor 1 (TNFR1). The pleiotropic TNFα initiates signaling down multiple canonical proinflammatory pathways and a particular role for the MAPK pathways has been implicated in mediating the anti-lipolytic effects of TNFα. Of the three known MAPK, namely p44/42, c-Jun N-terminal kinase (JNK), p38, only p44/42 and JNK are necessary for TNFα-induced inhibition of lipolysis.

In addition to impacting lipolysis, TNFα alters FFA synthesis in the liver. In fact, this effect is so potent that TNFα has been implicated in the etiology of hepatic steatosis, also known as non-alcoholic fatty liver disease. Endo et al. found that TNFα acutely and robustly accelerated fat accumulation in mouse liver. Additionally, mice treated with lipopolysaccharide (LPS), which activates immune pathways, similarly induced hepatic fat accumulation. However, further implicating TNFα, pretreatment of mice with an anti-TNFα antibody attenuated these deleterious effects. An important factor in hepatic fat synthesis is the sterol regulatory element binding protein-1c (SREBP-1c), which synthesizes a host of lipogenic enzymes. SREBP-1c mediates hepatic lipogenesis in response to both TNFα and LPS. Interestingly, TNFα may explain risk of developing fatty liver in humans. In analyzing a cohort of humans with steatosis, Tokushige et al. observed that those with advanced hepatic steatosis had elevated TNFα receptors.

**Hypertension**

The role of inflammation in causing hypertension involves several possible mechanisms, both direct and indirect. Focusing on a direct mechanism, CRP inhibits formation of nitric oxide by endothelial cells, which could promote vasoconstriction, platelet activation, oxidation, and thrombosis. An additional direct effect may be the CRP-induced upregulation of angiotensin receptors and enhanced plasminogen activator inhibitor-1 expression in endothelial cells, all of which could induce atherogenesis and elevate blood pressure. Indirectly, inflammation can result in hypertension via inflammation-induced insulin resistance. Insulin is a powerful vasodilator and a loss of insulin sensitivity leads to reduced vasodilation. Scheede-Bergdahl et al. found that vasodilation in response to prolonged insulin infusion is lessened in individuals with type 2 diabetes. Importantly, they note that this difference is not a result of diminished vascular capacity since non-insulin vasodilators cause similar forearm blood flow responses in both type 2 diabetic and non-diabetic subjects. Interestingly, in patients with the metabolic syndrome, hyperinsulinemia does not enhance responsiveness to vasodilators, suggesting the importance of effective insulin responsiveness in vasodilation.
Insulin Resistance

Due to the magnitude of published research exploring the relationship between inflammation and insulin resistance, as well as the robust role of insulin resistance in the metabolic syndrome (discussed later), special emphasis is warranted.

The pioneering discovery by Hotamisligil et al. that gave rise to the exploration of inflammation and obesity was centered around the observation that excess adipose tissue yields a pro-inflammatory state via pro-inflammatory secretagogues that induce systemic insulin resistance. The landmark paper was soon followed by evidence mechanistically linking inflammatory pathways with altered insulin receptor signaling. Briefly, normal insulin signaling initiates phosphorylation of tyrosine residues of the insulin receptor substrate-1 (IRS-1) subsequent to activation of the insulin receptor. This and other proximal signaling events are reduced in response to insulin in obesity and was considered to be the central dysfunction underlying insulin resistance. The altered insulin signaling in response to inflammatory mediators like TNFα involved the phosphorylation of IRS-1 on serine residues. Whereas tyrosine phosphorylation propagates the insulin signal downstream of IRS-1, serine phosphorylation stops the signal in its tracks, preventing downstream signaling and reducing insulin’s effects. However, cognizant of the fact that TNFα alone is not sufficient to explain IRS-1 serine phosphorylation, efforts continued to find the mediating kinase. Several have been implicated, namely JNK, the inhibitor of κB kinase β (IKKβ), and protein kinase C (PKC).

JNK is a well-known serine kinase and its activation in response to inflammatory signals and obese states prompted further research. Not only are JNK-deficient mice resistant to obesity-induced insulin resistance, but TNFα-induced IRS-1 serine phosphorylation is also prevented when JNK activity is blunted. Nuclear factor κB (NF-κB) is a primary transcription factor responsible for synthesis of a host of inflammatory cytokines. For NF-κB to function, it must be liberated from its cytosolic jailer by the action of IKKβ (i.e. when IKKβ is active, NF-κB is active). Distinct from its indirect role in initiating cytokine transcription, IKKβ, a serine kinase, is upregulated in obesity and IKKβ null mice are protected from diet-induced insulin resistance. Moreover, Yuan et al. revealed that inhibition of IKKβ improved insulin signaling by preventing IKKβ-mediated IRS-1 serine phosphorylation.

The PKC family is large and involved in many processes as second messengers. Certain PKC isoforms (β and δ) are implicated in mediating fatty acid–induced insulin resistance via serine IRS-1 phosphorylation, while another isoform (ε) enhances the inhibitory effect of TNFα on insulin signaling. TNFα is thought to induce PKCε translocation to the cell membrane, placing it in proximity to IRS-1 and serine phosphorylating and ultimately inhibiting IRS-1. A commonly cited pathway that activates PKC is the formation of the lipid diacylglycerol (DAG), though the inhibitory effect of DAG-activated pathways...
Insulin Resistance and Metabolic Syndrome

The distinct factors of the metabolic syndrome are often present in groups, with many people having more than one of the conditions. This phenomenon suggests a common abnormality rather than coincidence. The parallel increase in prevalence among populations of the metabolic syndrome and insulin resistance is not coincidental. Indeed, the association is so tight that the metabolic syndrome is also known as the “insulin resistance syndrome”, which questions where insulin resistance fits in defining the metabolic syndrome. Is insulin resistance merely one of many factors that identify the metabolic syndrome or is it fundamentally responsible in the pathogenesis of the other factors (Figure 1)? It seems the latter may be the case.

Central Obesity

A conversation regarding obesity and insulin resistance can be confusing and cyclical. For the sake of brevity, a popular concept is that obesity precedes insulin resistance (via inflammatory pathway activity, see above); though evidence certainly exists that insulin resistance can exacerbate obesity. An interesting example is the reduced hypothalamic sensitivity to insulin and leptin in response to diets high in saturated fats (palmitic acid), which inhibits insulin’s and leptin’s ability to regulate appetite and body weight. Interestingly, this effect is less pronounced in diets high in mono-unsaturated oleic acid, which fails to induce insulin resistance.

Dyslipidemia

Of the multiple insulin-sensitive tissues in the body, evidence suggests that muscle and liver insulin resistance may play a role in mediating dyslipidemia, albeit to varying degrees, with the liver being a dominant factor. Regarding the relatively minor role of muscle insulin resistance, Peterson et al. found that muscle insulin resistance reduces glycoen formation, redirecting carbohydrates to the liver for de novo lipogenesis with eventual increases in circulating lipids. Thus, even muscle-derived dyslipidemia requires the actions of the liver.

Hepatic insulin resistance is an interesting phenomenon. Whereas some insulin-dependent functions are indeed affected with hepatic insulin resistance, such as gluconeogenesis, other functions, such as hepatic lipogenesis, remain potently influenced by insulin, which explains the liver’s ability to synthesize new lipids from carbohydrate spill-over from the muscle despite identifiable insulin resistance. Li et al. identified the mTORC1 complex as the point of bifurcation, which is required for insulin-mediated increase in lipogenesis, but is not necessary for insulin-stimulated suppression of gluconeogenesis. Further, to identify the specific role of hepatic insulin resistance, independent of other peripheral factors, Biddinger et al. found that mice lacking the liver insulin resistance, which exhibit pure hepatic insulin resistance, develop a heavily proatherogenic lipoprotein profile, with reduced HDL cholesterol and increased VLDL cholesterol levels. Moreover, when fed a high-fat diet, in addition to exhibiting pronounced hypercholesterolemia, 100% of mice lacking a liver insulin receptor developed severe atherosclerosis.

Hypertension

Roughly half of all individuals suffering with hypertension are insulin resistant and severity of insulin resistance accurately predicts blood pressure. Indeed, Baron et al. found almost 20 years ago that insulin sensitivity is inversely correlated with blood pressure. These findings were soon followed with evidence highlighting how insulin impacts vasodilation (via increased nitric oxide release). Interestingly, in a reversal of supposed roles, while virtually all research on the effects of nitric oxide focus strictly on vasodilation, it may also impact insulin sensitivity. Mice with targeted disruptions in endothelial and neuronal nitric oxide synthase, which suffer from hypertension, experience significantly reduced total and hepatic insulin sensitivity, suggesting that nitric oxide plays a role in modulating insulin function and carbohydrate metabolism.

Conclusion

The metabolic syndrome is a prevalent problem worldwide, affecting upwards of 20%-60% of adults in countries of the Asia-Pacific region. The sustained surge of individuals suffering from the metabolic syndrome has grabbed the attention of biomedical scientists who seek to better understand its origins. A fruit of these labors is the discovery of the intimate relationship between the metabolic syndrome and chronic inflammation. While it is well established that inflammation plays a prominent role in the etiology of the metabolic syndrome, this may perhaps be true only insofar as inflammation induces insulin resistance, with insulin resistance serving as the prime mediator of inflammation-induced metabolic disturbances. With our current knowledge, future research efforts will reveal effective treatments to address the intertwined roles of inflammation and insulin resistance with a concentration on the treatment and prevention of the metabolic syndrome.
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Benjamin Bikman began his academic career studying Exercise Physiology at Brigham Young University in Utah, USA from 1999-2005. While there, Dr. Bikman’s research interests subtly shifted. Rather than exploring the mechanisms that mediate the cellular adaptations to exercise, he began to focus on the molecular mechanisms that are altered with adaptations to obesity. He completed his thesis exploring the effects of aging and exercise on the chronic systemic inflammation that accompanies weight gain and obesity. He then joined the laboratory of G. Lynis Dohm at East Carolina University in North Carolina, USA where he obtained his doctoral degree in Bioenergetics. His dissertation work focused on the exploration of obesity- and inflammation-induced insulin resistance, concentrating particularly on the interaction between the metabolic and immune systems. Following his doctoral degree in 2008, Dr. Bikman sought to work with Dr. Scott Summers, a leader in the area of insulin resistance, who was at the University of Utah where he then moved his lab to Duke-NUS in Singapore. While at Duke-NUS, Dr. Bikman continued to focus on insulin resistance and helped establish the current paradigm of the etiology of obesity-induced insulin resistance. Dr. Bikman very recently joined the faculty of his alma mater and is an Assistant Professor in the Physiology and Developmental Biology Department at Brigham Young University.

M. Andrew Bressler, an undergraduate at Brigham Young University in Molecular Biology, works as a student research assistant in the Laboratory of Obesity and Metabolism under Dr. Bikman. His future plans include medical school and a career as an ophthalmologist where he hopes to make a difference. Andrew grew up in Rexburg, Idaho as part of a close family consisting of his parents and five siblings. Andrew believes that molecular approaches and methods will constitute much of the future of medicine in order to better diagnose and treat diseases.
Autophagy and its Role in Metabolism

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Macroautophagy (hereafter autophagy) is a cellular quality control mechanism that evolved to recycle cellular waste and maintain energy homeostasis under starvation. However, its implications in regulating metabolism has only recently begun to be uncovered. Recent studies have revealed new functions of autophagy such as sensing damaged tissue mitochondria and preventing cellular injury by removing redundant protein aggregates. Moreover, the observation that autophagy regulates lipid metabolism has widened our understanding of the delicate and indispensable role autophagy plays in cellular metabolism and holds promise of a relatively new and exciting strategy for treating metabolic disorders.

Cellular Mechanics of Macroautophagy

The molecular mechanism for autophagy has been mainly uncovered by studies in yeast S. cerevisiae. To date, genetic studies of S.cerevisiae have revealed over 30 genes involved in autophagy (ATG; Autophagy-related gene), with 18 genes that are essential for autophagosome formation. Importantly, most ATG genes are well conserved in mammals, and have similar functions as their corresponding proteins in yeast. During macroautophagy, intact organelles (such as mitochondria) and portions of the cytosol are sequestered into a double-membrane vesicle, termed an autophagosome, which subsequently fuses with an endosome and/or lysosome, to form an autolysosome. This latter step exposes the cargo to lysosomal hydrolases to allow its breakdown, and the resulting macromolecules are transported back into the cytosol through membrane permeases for reuse (Figure 1). Among these Atg proteins, one subset is essential for autophagosome formation, and is referred to as the "core" molecular machinery for autophagy. These core Atg proteins are composed of four subgroups: (a) The Atg1/unc-51-like kinase (ULK) complex; (b) two ubiquitin-like protein (Atg12 and Atg8/LC3) conjugation systems which involve conjugating proteins like Atg7 and Atg10; (c) the class III phosphatidylinositol 3-kinase (PtdIns3K)/Vps34 complex I; and (d) two transmembrane proteins, Atg9/mAtg9 (and associated proteins involved in its movement such as Atg18/WIPI-1) and VMP1. The proposed site for autophagosome formation,
where most of the core Atg proteins are recruited, is termed the phagophore assembly site (PAS).

### Metabolic Regulators of Autophagy

Autophagy is a stress-induced catabolic process that is tightly regulated by two major energy and nutrient sensing signaling pathways:

1. **mTOR (mTORC1) pathway:** Nutrient starvation, stress, or reduced availability of growth factors alarm eukaryotic cells to adjust their metabolism in order to survive. Among the numerous components involved in the regulation of autophagy and growth, mTORC1 (mammalian target of rapamycin) is a key component that coordinates the balance between growth and autophagy in response to intracellular and environmental conditions. The activity of mTORC1 is inhibited under nutrient starvation, which is a crucial step for autophagy induction in eukaryotes. Recent studies indicate that, the first signaling component downstream of mTORC1 in the autophagy pathway is Atg1, an evolutionarily conserved serine/threonine kinase. Atg1 likely plays a key role at the earliest step in the initial stages of autophagy induction such as the nucleation (the early event when membrane structures are initiated) and formation of the preautophagosomal structures (PAS). mTORC1 inhibits Atg1 (or ULK1) by either phosphorylating its activators like Atg13 at multiple residues causing a reduced affinity between Atg1 and its binding proteins, or by phosphorylating Atg1 itself leading to repression of autophagy. Hormonal inhibition and stimulation of autophagy by insulin and glucagon, respectively leads to opposing regulation of mTORC1 in fed and starved states.

2. **AMPK Pathway:** The AMP-activated protein kinase (AMPK) is another sensor of cellular bioenergetics, specifically in response to energy stress. During nutrient and energy depletion, AMPK is activated by a decreased ATP/AMP ratio through the upstream LKB1 kinase (encoded by the Peutz-Jeghers syndrome gene). Active AMPK leads to inhibition of mTORC1 activity either via phosphorylation of TSC1/2 or phosphorylation of Raptor, a subunit of mTORC1. Thus, AMPK serves as a positive regulator of autophagy. Research by the Shaw and Guan groups show yet another, more direct, mechanism whereby AMPK regulates autophagy through phosphorylation of ULK1. Taken together, these findings increase our understanding of the mechanisms that connect cellular energy homeostasis and autophagy.

### Metabolic Roles of Autophagy

1. **Mitophagy (autophagy of mitochondria):** While mitochondria perform essential functions for the cell, notably ATP production via oxidative phosphorylation, any damage to the mitochondrial outer membrane leads to release of cytochrome c, triggering caspase activation and apoptosis. More catastrophic stresses can lead to pathologic increase in mitochondrial permeability, accompanied by transient but massive release of reactive oxygen species (ROS) and calcium. These events can trigger neighboring mitochondria to do the same, culminating in activation of calcium-dependent proteases (calpains) and lipases (cPLA2) that together ensure the necrotic destruction of the cell. Impaired mitochondrial function has been suggested to be a significant pathophysiological process. Indeed, the accumulation of intracellular fatty acids and diacylglycerol, which may cause mitochondrial dysfunction can ultimately lead to suppression of insulin sensitivity. Therefore, a defect in mitochondrial function may be responsible for cellular insulin resistance. Moreover, since mitochondrial dysfunction has been found to occur in organs such as skeletal muscle, liver, pancreas and smooth vascular cells, mitochondrial dysfunction could play a critical role in the occurrence of metabolic...
diseases. Autophagy of mitochondria helps to reduce mitochondrial stress by recycling damaged mitochondria before they can trigger an apoptotic cascade thus preventing tissue damage. In fact, livers of Atg7 deficient mice develop massive hepatomegaly (enlarged liver) marked by accumulation of deformed mitochondria. The regulation of ULK-1 by AMPK has been proposed to link mitochondrial damage to mitophagy.

2. Removing Protein Aggregates: Continuous removal of unfolded and redundant proteins is necessary for the survival of non-dividing cells such as neurons and hepatocytes since they accumulate these protein aggregates during their long life span. Notably, Atg7 null mice that have defective autophagy accumulate polyubiquitinated proteins that can lead to hepatomegaly. One such aggregated protein, p62/SQSTM1 may induce increased oxidative stress and even tumorogenesis. Similarly, stimulation of autophagy has shown to be beneficial in the treatment of genetic disorders like α1-antitrypsin deficiency in which protein aggregate formation occurs in the liver.

3. Lipid and Carbohydrate Metabolism: Fatty acids are essential to all organisms — as substrates for energy production. They are stored as triglycerides in highly dynamic cytoplasmic organelles called lipid droplets and, when necessary, are re-released by the process of lipolysis. Although cytosolic lipases were considered to be the only mechanism of catalyzing lipid droplets in adipose tissue, their relative scarcity in tissues such as liver raised the question of whether other mechanisms of lipolysis exist within these cells. Studies by Singh et al. demonstrated that hepatocytes catalyze lipid droplets through an autophagic process termed as "lipophagy" which was later also identified as a key pathway for cholesterol efflux in macrophage foam cells. The released free fatty acids can be directly utilised for energy production in hepatic mitochondria. In contrast, autophagy is required for the production of the large lipid droplets in white adipose tissue. Inhibition of autophagy blocks white adipocyte differentiation. In fact, adipose-specific knockout of Atg7 results in mice that have white adipocytes manifesting features typical of brown adipose tissue. Consistent with the rapid energy burning characteristic of brown adipocytes, these mice are lean. However, they are not healthy since they are at increased risk of early death when fed either a regular or high-fat diet.

Similarly, Ezaki et al. reported that hepatic autophagy in mice contributes significantly to the maintenance of blood glucose by converting amino acids to glucose via gluconeogenesis. Under certain fasting conditions, autophagy is induced concomitantly with a fall in plasma insulin in the presence of stable glucagon levels, resulting in robust amino acid release. In liver-specific Atg7-deficient mice, no amino acid release occurs in response to starvation and blood glucose levels continue to decrease in contrast to that of wild-type mice. Autophagy is also essential for the health of pancreatic β-cells and enables their expansion in response to a high-fat diet. In the liver, defective autophagy leads to insulin resistance and its restoration through retroviral expression of Atg7 leads to recovery of their insulin sensitivity.

Pathophysiology of Defective Autophagy:

1. Pancreatitis: Acute pancreatitis is an inflammatory disorder that is believed to be initiated by self-digestion of the pancreatic acinar cells following inappropriate activation of enzymes, particularly trypsin. In a normal acinar cell, autophagy mediates the degradation of trypsinogen-containing zymogen granules that are not secreted from the apical membrane. In pancreatitis, a block in enzyme secretion leads to an accumulation of intracellular zymogen granules, which result in increased uptake of these structures by autophagosomes. Following autophagosome-lysosome fusion, degradation of cargo fails to occur. Active enzymes from these enlarged autolysosomes are released into the cytoplasm to initiate pancreatic cellular injury.

2. Alcoholic and Non-Alcoholic fatty liver disease: Recent studies have shown that alcoholic injury of the liver is associated with an up-regulation of autophagy. Increased autophagy serves as a protective stress response to injury and is selective towards removing damaged mitochondria and lipid droplets. Similarly, defective autophagy is thought to be a major cause of non-alcoholic fatty liver disease (NAFLD). Lipid degradation by autophagy or "lipophagy" may be inhibited by chronic hepatic lipid overload leading to steatosis and insulin resistance.

3. Cellular injury and tumorigenesis: Basal levels of autophagy are also required for maintenance of pancreatic β-cells and hepatocytes in the mammals. Loss of autophagy is associated with mitochondrial abnormalities and large aggregates of polyubiquitinated proteins, including p62. Interestingly, increased accumulation of p62 also has been shown to be the key initiator of tumorgenesis in autophagy-deficient livers. Similarly, basal autophagy can protect plaque cells against oxidative stress by degrading damaged intracellular material, in particular polarized mitochondria. In this way, successful autophagy of the damaged components promotes cell survival and may reduce cardiovascular complication associated with atherosclerosis.

Conclusion

Autophagy is a major contributor to cellular metabolism and survival. It serves to provide fuel for energy production under starvation while monitoring and clearing damaged and non-functional organelles; thus providing an essential means for refreshing and remodeling cells. It is required for normal development, especially for metabolic tissues such as adipose tissue and pancreatic β-cells. At the physiological level, autophagy promotes metabolic homeostasis and prevents degenerative disease and cancer and thus opens a new field of therapeutic intervention for the treatment of metabolic disorders, as summarized in Table 1.
## Metabolic diseases potentially involving Autophagy

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>PATHOPHYSIOLOGIC CONSEQUENCES</th>
<th>THERAPEUTIC INTERVENTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>Decreased insulin production and hepatic insulin resistance</td>
<td>Increasing autophagy may help expand β-cell mass, provide resistance against stress and enhance hepatic insulin sensitivity.</td>
</tr>
<tr>
<td>Nonalcoholic fatty liver disease</td>
<td>Increased steatosis, hepatocyte injury and predisposition to cirrhosis and hepatic cancer</td>
<td>Increasing autophagy would help getting rid of liver fat and inflammation together with protection against tumorogenesis.</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>Increased cellular injury due to defective autophagy</td>
<td>Decreasing autophagy may help to prevent or treat pancreatitis.</td>
</tr>
<tr>
<td>Cardiovascular complications</td>
<td>Atherosclerosis</td>
<td>Increasing autophagy may safeguard plaque cells against cellular distress, in particular oxidative injury.</td>
</tr>
<tr>
<td>Hypercholesterolemia, Hypertriglyceridemia</td>
<td>Increased circulating and tissue cholesterol and triglycerides</td>
<td>Increasing autophagy may help to degrade hepatic triglyceride and regulate reverse cholesterol transport (RCT) from the macrophage.</td>
</tr>
<tr>
<td>Obesity</td>
<td>Hypertrophy in white adipose tissue</td>
<td>Regulated decrease in autophagy could be beneficial in limiting white adipose tissue mass and lipid content.</td>
</tr>
</tbody>
</table>

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Human Cancer Viruses: Past, Present and Future

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In 2008, cancer caused 7.6 million deaths worldwide. Several factors increase the risk of developing cancers such as smoking for lung cancer or sun exposure for melanoma. Infection by viruses is the second leading cause of cancers. It has been estimated that approximately 12% of all cancers worldwide are attributable to viral infections [1]. Cancer causing viruses are termed oncoviruses, and it is of interest to learn more about them.

DNA and RNA Oncoviruses

Oncoviruses can be DNA or RNA viruses (Table 1). To date, the DNA viruses which have been implicated in the etiology of human cancers include human papilloma viruses (HPVs), Epstein–Barr virus (EBV), Kaposi’s sarcoma-associated herpesvirus (KSHV), hepatitis B virus (HBV) and the Merkel cell polyomavirus (MCV). Among the RNA viruses, hepatitis C virus (HCV) and the human T-cell leukemia virus type 1 (HTLV-1)-retrovirus are associated with human malignancies [2]. Infection with another retrovirus, human immunodeficiency virus (HIV), although associated with an excess of cancer incidence, is probably not carcinogenic per se, but acts mainly via immunodeficiency [3]. Except for MCV which remains under further study, all these mentioned viruses have been classified as group 1 carcinogens by the International Agency for Research in Cancer (IARC) [4].

IARC considers that there is convincing evidence that infection with HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 or 66 leads to cervical cancer [5]. These HPV types can be sexually transmitted. HPV 16 and HPV 18 are the most pathogenic and account for approximately 70% of cervical cancers [3], which are diagnosed yearly in nearly 0.5 million women worldwide claiming 0.25 million lives. Evidence supports a contributory role for HPV 16 and 18 in cancers of the vulva, vagina, penis, anus, oral cavity, oropharynx, larynx, and periangual skin. Collectively, all HPV infections account for approximately 5% of total cancers globally [5].

Epstein–Barr virus (EBV or HHV-4), initially identified in 1964, was the first herpesvirus shown to be oncogenic in humans.
Establishing a direct, indirect or cofactor etiologic relationship between EBV and cancers is more difficult than HPV because of the ubiquitous presence of EBV in the general population [3]. EBV is associated with four types of cancers: Burkitt’s lymphoma (one of the most dreaded diseases in sub-Saharan Africa), Hodgkin’s lymphoma, nasopharyngeal carcinoma (the most common tumor of males in southern China), and non-Hodgkin lymphoma associated with post-transplant or HIV immunosuppression [3, 6, 7].

Unlike EBV, KSHV, also called human herpesvirus 8 (HHV-8), is not ubiquitous, only 5% of the general population are infected with this virus. In the early 1990s, the increased incidence of Kaposi’s Sarcoma (KS) was one of the first obvious manifestations of the acquired immunodeficiency syndrome (AIDS) epidemic. The KSHV virus was subsequently identified and isolated from a case of AIDS-associated KS in 1994. This virus is most probably transmitted via oral exchange of infected saliva; it is rarely detected in semen. Both sexual and non-sexual transmissions are possible. Diseases associated with KSHV include Kaposi’s sarcoma (the most common malignancy affecting individuals with HIV/AIDS), primary effusion lymphoma (PEL), and multicentric Castleman’s Disease (MCD) which, although not formally a malignancy, can evolve into one [7].

HBV is a small DNA virus that can be transmitted from human to human vertically, through close personal contact, through contaminated blood and blood products, or sexually. An effective HBV-vaccine has been available for the last twenty years; however, approximately 360 million people worldwide are still chronic carriers. HCV is a single-stranded RNA virus that is transmitted mostly from unscreened blood transfusions or invasive medical procedures using contaminated equipment. The World Health Organization estimates that 170 million people are infected worldwide, but this number is apparently increasing. Liver cancer or hepatocellular carcinoma is the sixth most common cancer in the world; but ranks third in terms of mortality, due to its very poor prognosis. It is estimated that 54% and 31% of the world total liver cancer cases are attributable to HBV and HCV infection, respectively [3]. The development of hepatocellular carcinoma is slow generally occurring more than 30 years after infection with HBV or HCV [8].

In 2008, Feng et al. [9] discovered MCV, a previously unknown polyomavirus in 80% of Merkel cell carcinoma (MCC) (a rare but highly aggressive neuroendocrine skin malignancy that affects elderly and immunosuppressed patients). MCV was demonstrated to be monoclonally integrated into the host genome in MCC, suggesting that viral infection precedes clonal expansion of the tumor. Because viral genome integration is one of the typical features of virus-mediated oncogenesis, MCV is thought not to be a passenger virus but to play a causative role in tumorigenesis [10].

HTLV-1 was the first identified human retrovirus isolated in 1980 and 1981 from American and Japanese patients suffering from adult T-cell leukemia (ATL), a rapidly fatal disease. Since then, a causal association between the virus and the malignancy has been firmly established. Viral transmission mostly occurs from mother to child through breast-feeding, sexually through partners, or iatrogenically via transfusion of infected blood products. HTLV-1 infection is endemic to certain regions, including Southern Japan, the Caribbean basin, Central and South America, and Central Africa. It is estimated that 15–20 million people worldwide are chronic HTLV-1 carriers of whom 1–5% have lifetime risk of developing ATL [1].

Viral causality of human cancers

The relationship between viruses and cancers has long intrigued researchers. The acceptance of a virus–cancer association was initially difficult because viruses were perceived as infectious and transmissible whereas cancers were not. Traditionally, the application of Koch’s postulates for disease etiology requires the demonstration that a specific microbiologic agent is responsible for an infectious disease. Koch’s postulates are, however, difficult to apply to viral diseases. Asymptomatic virus infection and carriage are the norm for most tumor viruses which complicates Koch’s third principle that the cultured microorganism should cause disease when introduced into a healthy organism. It is therefore necessary to develop different criteria for the viral etiology of human cancers. A major complication resides with
the reality that some viruses cause tumors directly while other viruses contribute to tumorigenesis only indirectly.

If the virus has a direct role in cellular transformation, the following criteria can be applied:
1) the consistent presence of the viral DNA in tumor biopsies and the persistence of this DNA in cell lines derived from these tumors; 2) the demonstration of growth-promoting activity of specific viral genes or of virus-modified host cell genes in tissue culture or animal models; 3) the demonstration that the malignant phenotype depends on the continuous expression of viral oncogenes or on the modification of host cell genes containing viral sequences; 4) epidemiological evidence that the respective virus infection represents a major risk factor for cancer development [2].

If the virus acts indirectly for tumorigenesis, it is more difficult to define stringent criteria. Indeed, rather than inserting viral oncogenic genes into the host cell or modulating existing cellular oncogenic genes (proto-oncogenes), indirect tumor viruses modify the cellular context to facilitate changes in cell growth. For example, the virus can trigger immunodeficiency facilitating other carcinogenic events such as concurrent viral infection or chronic inflammation. For indirect oncogenic viruses, the disease association is determined by epidemiological data, experimental results explaining possible modes of virus-host interaction, and by clinical observations. The association between virus and cancer thus becomes more a question of plausibility than stringent experimental deduction.

### Mechanisms of direct versus indirect causality

As mentioned above, human oncoviruses can cause tumors in two ways, direct or indirect. In the direct route, some viruses integrate their viral genome into that of the host cell. The integrated virus can activate nearby cellular oncogenes and/or inactivate tumor suppressor genes leading to cellular transformation with increased proliferative fitness of the cell. Transformed cells have increased cell growth rates and loss of growth inhibition, a limitless replicative potential, and changes in cellular morphology and metabolism. However, the mechanisms used by different viruses to cause cancer are various and complex.

Persistent infection with directly transforming oncoviruses such as HPV 16 and 18 is accompanied by the integration of viral sequences into human chromosomes. This integration may disrupt the normal transcription of some genes such as the cellular oncogene c-myc [2] to cause cancer. EBV and HHV8 produce viral proteins with homology to known cellular proto-oncoproteins. These viral mimics of cellular proteins induce immune evasion, inhibit apoptosis, and change cell growth by affecting the expression of many host genes [11]. For HTLV-1, several studies have shown that the expression of viral Tax protein is necessary and sufficient to cause leukemia. Recent data suggest that in vivo carcinogenesis caused by Tax also correlates with its propensity to trigger tissue inflammation [12].

Indirect viral oncogenesis can also occur in various ways. Carcinogenesis can arise by immunosuppression and by chronic nonspecific inflammation occurring over decades. It is generally thought that HBV and HCV transform tissues indirectly through the induction of chronic inflammation in the affected liver perhaps via the production of reactive oxygen radicals. In a similar vein, HIV infection likely contributes indirectly to the development of KS cancers via immunosuppression [3].

### Comorbidities and multistep progression in tumorigenesis

Oncoviral infection of cells are much more common than the cancers that arise from infected cells suggesting that infection per se is insufficient for tumor development and that tumorigenesis requires the contribution of several factors in a multistep process. Thus, the progression of HPV-associated squamous-cell epithelial lesions to cervical cancer is enhanced by comorbid agents such as herpes simplex virus or Chlamydia or concurrent immunodeficiency. Other risk factors include smoking, high numbers of pregnancies, first pregnancy at young age, and use of oral contraceptive [3]. The immunosuppressive effects of malarial infection have been proposed to activate EBV-associated lymphoproliferation [6], and ambient exposure to potential carcinogens such as salted fish containing nitrosodimethylamines and perhaps inhaled herbal extracts have been implicated as possible cofactors in EBV-associated nasopharyngeal carcinoma. Similarly as noted above, HIV infection contributes to KS via immunosuppression. Accordingly, effective highly active antiretroviral therapy (HAART) of HIV has caused a decline in the incidence of KS in Western countries [5].

In a multistep process, only some infected cells will complete all the steps to achieve transformation. This notion fits with the observation that only a fraction of virus infected cells become cancerous. Indeed, a succession of changes which confer cell growth advantage is seen in the process of cellular transformation [13]. For example, some of these stepwise changes for leukemogenesis caused by HTLV-1 include damaged cellular chromosomal DNA and abnormal chromosome numbers (aneuploidy). Similar changes are also seen in HPV-transformed cells. However, a distinction exists amongst different oncogenic viruses; some act to simply initiate the transformation of cells while others are needed to initiate and maintain the transformed cells. Thus, sixty to seventy percent of late stage HTLV-1 induced ATLs appear to become virus independent leukemias that do not express viral proteins [12] while all late stage HPV cervical tumors still require the expression of two HPV oncoproteins, E6 and E7, for the maintenance of the cancer.

### Unanswered questions and future challenges

Although HCC is the most common cancer associated with HCV infection, two other malignancies are also seen
with this virus. It has been suggested that HCV may also be a risk factor for the onset of cholangiocellular carcinoma. In HCV patients, the risk of cholangiocellular carcinoma is estimated to be increased by 2.6 times. Because cholangiocellular carcinoma and hepatocellular carcinoma may arise from the same progenitor cells, a common mechanism(s) may account for both types of malignant transformation [8]. The second HCV associated disease is cryoglobulinaemia (MC), a lymphoproliferative disease that can evolve into B-cell non-Hodgkin lymphoma (NHL). This pathology may be under-reported and possibly underdiagnosed in HCV-infected patients [8] because few studies have evaluated the association between HCV infection and NHL [3]. Several other associations between viral infections and human cancers remain to be considered. In primary central nervous system (CNS) malignancies, polyomaviruses have been detected with varying frequencies in a number of pediatric and adult tumor subtypes. Three polyomaviruses that have been detected most frequently in both pediatric and adult primary CNS brain tumors are the JC virus (JCV), BK virus (BKV), and Simian virus 40 (SV40). However, actually establishing a link between chronic viral infection and primary CNS malignancy is an area of considerable controversy, due in part to variations in detection frequencies and methodologies used among researchers. Highlighting these difficulties are recent findings whereby a previously proposed link between SV40 and lung cancer now appears largely disproven [14, 15] and a reported association between XMRV and human prostate cancer appears also in doubt [16]. Both SV40 and XMRV are non-human animal viruses. While their roles in human cancers are now mostly unsubstantiated, it remains possible that other animal viruses could in the future cross the species barrier to become new tumorigenic agents in humans.

**Concluding remarks**

Viral infections represent an area of cancer research which has made significant advances in the last 30 years. In 1981, only two viruses were thought to cause human cancers. Now, the oncogenic roles of eight viruses are well-established [17]. It is likely that many other viral infections that may be oncogenic in humans remain to be unveiled. Because oncogenic viral infection can be prevented with vaccines (safe and effective HBV and HPV vaccines have been developed), it is imperative that we redouble our efforts to identify and characterize viral etiologies of human neoplasias.

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**Serpiginous Choroiditis: An Update**

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**Table 1: Different nomenclatures of Serpiginous choroiditis by various authors**

- Peripapillary choroidal sclerosis by Sorsby, 1939
- Helicoid peripapillary chorioretinal degeneration by Franceschetti, 1962
- Geographic helicoids peripapillary choroidopathy by Schatz, 1974
- Geographic choroiditis by Baarsma, 1976
- Serpiginous choroidopathy by Gass, 1987

Serpiginous choroiditis is a rare cause of posterior uveitis, usually less than 5% in most of the studies from the world. It has been reported in various studies that the incidence of serpiginous choroiditis is higher in India (Table 2). The disease affects healthy, young to middle aged adult with higher male predominance. Though there is no familial predisposition, in one study the clinical entity was found to be associated with HLA B7.

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**Geographic Helicoid Peripapillary Choroidopathy (GHPC)** is a rare, usually bilateral, chronic, progressive and recurrent disease of unknown aetiology affecting the retinal pigment epithelium, choriocapillaris and choroid. It characteristically starts at the juxtapapillary or peripapillary region and progresses centrifugally from the disc to involve the macula area. It is also known as serpiginous choroiditis because of its peculiar extension in a serpiginous fashion. The disease has a relentless destructive course. As the lesions resolve, retinal pigment epithelial and choroidal degeneration begin, leading to fibrous scarring and pigment hyper or hypoplasia. Subretinal neovascular membrane (SRNVM) formation may occur after a chronic course. On rare occasions, serpiginous choroiditis may present initially as lesions involving the macula exclusively.

The word "serpiginous" is an adjective which means “with a wavy or indented margin”. The serpiginous choroiditis shows the similar wavy or amoeboid like lesions in choroid as a result of inflammation of unknown aetiology. Jonathan Hutchinson first described this entity in 1900 in Archives of Surgery. This clinical entity was first reported by junius in 1932 who termed it as "peripapillary retinochoroiditis". Thereafter, this clinical entity has passed through various nomenclatures by various authors (Table 1). The term "serpiginous choroidopathy" was coined by Gass in 1987.
Aetiopathogenesis

The etiology of serpiginous choroiditis is unknown. Association of various infective agents has been implicated in aetiopathogenesis of this clinical entity. A role of possible viral aetiology has been suggested by Gass et al, who reported a case of serpiginous choroiditis following Herpes zoster. Priya et al reported that two-thirds of aqueous humor samples from patients with serpiginous choroiditis in their study were positive for varicella zoster virus (VZV) or herpes simplex virus (HSV) using the polymerase chain reaction. Gupta et al reported seven cases of ocular tuberculosis who presented with serpiginous choroiditis and showed considerable improvement in terms of visual acuity and clinically, when treated with antitubercular drugs. Laatikainen and Erkkila reported nine patients with serpiginous choroiditis and all of them had positive tuberculin skin tests. With advent of newer diagnostic tests like interferon (IFN-γ) release assays-QuantiFERON TB gold tests, the diagnosis of tubercular infection has become easier and more accurate. With the help of this test, Friederike et al reported that 11 of 21 serpiginous choroiditis patients (52%) were tested positive in their study, indicating a tuberculous etiology in this uveitis entity. There are also reports of an immune-mediated mechanism attributable to HLA-B7 and retinal S antigen associations. An elevation of factor VIII-von Willebrand antigen has been found in a small series of patients.

Table 2: Reported incidence rate of serpiginous choroiditis in various Indian studies

- Biswas et al (1997)-19%
- Gupta et al (2001)-25.1%
- Rathinam et al (2001)-10.9%
- Das et al (2005)-15.21%

Clinical Pictures

Serpiginous choroiditis is a bilateral condition with asymmetric involvement of the eyes. The patient typically presents with unilateral decrease in vision, photopsias, metamorphopsia, and visual field loss. On examination, the anterior segment is usually normal. If present, the vitritis is mild and most often in the form of pigmented cells in anterior vitreous. Serpiginous choroiditis involves the peripapillary region and macula. Recurrences are common and can occur weeks to years after the initial event. Depending on the extent of lesions, serpiginous choroiditis can be divided into the following types:

Classic or Peripapillary Geographic Serpiginous choroiditis

Classic or Peripapillary Geographic variety accounts for 80% cases of serpiginous choroiditis. The lesion begins with ill-defined patches of grayish or creamy yellow subretinal infiltrates which starts at the peripapillary area and progresses towards the periphery like a serpentine in a centrifugal manner (Figure 1,2). The overlying retina is secondarily involved and becomes oedematous. Though rare, sometimes serous exudative detachment can occur. The active lesions generally resolve within 6-8 weeks with or without treatment, ultimately leaving behind areas of choriocapillaries and retinal pigment epithelium atrophy. Many a time, the disease remains asymptomatic until the fovea is affected. It has been seen that about two third of patients with serpiginous choroiditis may present with scars or healed lesions at the time of initial presentation.

Macular Serpiginous choroiditis

Macular variety, accounts for 5.9% cases of total serpiginous choroiditis cases. The lesion begins in the macular area and is characterized by worse visual prognosis due to foveal involvement and higher risk of secondary CNVM. This variety of serpiginous choroiditis often remains under-diagnosed or misdiagnosed.

Ampiginous Choroiditis

This is a rare variety of serpiginous choroiditis where the lesions generally occur in periphery in a multifocal pattern. Ampiginous choroiditis involves the periphery in a multifocal pattern. The lesions generally occur in periphery in a multifocal pattern.
choroiditis was first reported by Lyness and Bird in 1984, who described a recurrent form of acute posterior multifocal placoid pigment epitheliopathy (APMPPE) that resembles serpiginous choroiditis in its bilateral nature, fluorescein angiographic features, resultant pigmentary disturbances and the recurrent clinical course. The term "Ampiginous Choroiditis" was coined by Nussenblatt et al.

Compared to the classic variety of serpiginous choroiditis, there is no significant difference in anterior segment inflammation, vitritis in Ampiginous Choroiditis. However the central foveal involvement is less in Ampiginous Choroiditis.

Ancillary Tests

Fundus fluorescein angiography: FFA shows early hyperfluorescence of the active lesions. The late phase of the study demonstrates hyperfluorescence of the border of the active lesion that may extend centrally (Figure 7). Inactive lesions show early hyperfluorescence and progressive hyperfluorescence with late staining of the sclera and scar tissue.

Indocyanine Green angiography: ICG is often more sensitive than FFA in determining extent and appearance of new subclinical lesions. Some authors reported that the lesions which were not apparent on FFA can be detected with the help of ICG. Also ICG shows larger area of hypofluorescence in active lesions than seen clinically or on FFA. ICG in serpiginous choroiditis shows hypofluorescent areas beginning from early to late phase indicating non perfusion of the choriocapillaries and often areas of delayed filling, indicating late perfusion of the choriocapillaries.

Visual fields & Electrophysiological Studies: Visual field shows absolute or relative scotomas corresponding to the lesions. Electrophysiologic studies are usually normal.

Differential Diagnosis: Though serpiginous choroiditis is easy to diagnose from its characteristic lesions and pattern of involvement, few conditions which affect choriocapillaries like variety of macular lesions, that can mimic this variant form of serpiginous choroiditis. These include age-related macular degeneration, idiopathic subretinal neovascularization, idiopathic central serous retinopathy with exudation, retinal pigment epithelitis, posterior scleritis, toxoplastic retinitis, presumed ocular histoplasmosis syndrome, tuberculosis,
sarcoidosis, acute multifocal posterior placoid pigment epitheliopathy (APMPPE) and viral diseases. It is differentiated from serpiginous choroiditis for similar clinical and angiographic pictures as their management differs significantly.

Treatment

Depending on the various proposed theory of aetiopathogenesis, several treatments have been tried for serpiginous choroiditis.

Systemic corticosteroids are found to be effective in controlling the active lesions and shortening the duration of active diseases but their role in prevention of recurrence is doubtful. Serpiginous choroiditis has been reported to recur while tapering and discontinuation of systemic corticosteroids thereby emphasizing the role of long term corticosteroids therapy. However in cases of fovea-threatening lesions, aggressive rapid control of the inflammation is needed as it has been reported that the response of serpiginous choroiditis to oral steroids occurs after two weeks of treatment. So, high-dose intravenous steroid therapy (1g intravenous methylprednisolone daily for three days) is recommended by many authors for macula-threatening cases of serpiginous choroiditis. There are also reports of intravitreal Triamcinolone Acetate (IVTA) therapy in serpiginous choroidopathy. IVTA was also used in cases where systemic corticosteroids were contraindicated and in a case of secondary choroidal neovascular membrane. It has been observed that though IVTA injection brings in the required concentration of the drug without systemic side effects to the desired tissue level and likely to be effective in the treatment of acute lesions, but it is not helpful in preventing recurrence of the disease.

The spectrum of alternative therapies to systemic corticosteroid treatment ranges from immunosuppression with cyclosporine alone or as part of a regimen with immunosuppressives and most of the study using these agents showed mixed result. Christmas et al reported 4 out of 6 patients with serpiginous choroiditis in their study, who were treated with cyclosporine alone or combined with azathioprine experienced a recurrence while on therapy.

A triple-agent immunosuppressive regimen using cyclosporine (5mg/kg/day initially) in combination with azathioprine (1.5mg/kg/day) and prednisone (1mg/kg/day) was first reported by Hooper and Kaplan in 1991. Treatment was tapered 8 weeks after initiation and discontinued after 6 months, when no recurrence was encountered. However, as the medications were weaned, recurrence of the inflammation developed in two patients. Munteau et al also reported satisfying results with this triple-agent therapy. Although prompt control of the inflammation on initiation of treatment was achieved, recurrence of inflammation after discontinuation of treatment has been reported in some studies. Also, Biswas et al reported that there was no significant change in the rate of regression of lesions in their study when this regimen was compared to the treatment with azathioprine or corticosteroids alone.

There are also reports of use of Interferon Alpha used in management of Serpiginous choroiditis. Sobaci et al reported of successfully treating 8 eyes of 5 patients with IFN alpha-2a, but they could
not explain the mechanisms by which IFN affects the course of Serpiginous choroiditis. Continued progression of choroiditis lesions occurred in 14% of patients after initiating antituberculosis treatment in tubercular serpiginous-like choroiditis. Increased immunosuppression with continuation of antituberculosis treatment resulted in good outcome.43 Serpiginous choroidopathy was seen in young patients and had three distinct presentations that seemed to affect the choriocapillaris primarily. Patients appeared to have a variation of serpiginous choroidopathy, typical of the Asian-Indian population, that had some important differences from that reported in Caucasians.44 Prompt diagnosis and rapid initiation of treatment of active lesions with immunosuppression and maintenance of appropriate immunosuppression for at least 6 months is essential for initial management and prevention of recurrences in Serpiginous choroiditis.

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About the Authors

Dr Alok Agrawal graduated from India in 2003. After his undergraduate degree he went and did a long-term observership in different eye hospitals in USA. He received his Postgraduate degree from India in 2008 and PhD in Ophthalmology in 2011. He did his long term fellowship training in Uveitis in 2008 at Sankara Nethralaya, India and has acquired a wealth of experience in managing patients with a variety of complex ocular inflammatory diseases after doing another International Clinical Fellowship in Ocular Immunology & Inflammation Services from Singapore National Eye Center, Singapore in 2010.

His research interests are mainly in Vogt-Koyanagi Harada Disease, Cytomegalovirus infection in the immunocompetent. Dr Alok’s other passion is in uveitic cataract surgery.

Dr Alok is member of various eye societies and has numerous publications in peer review journals. He is actively involved in research and has given talks in various conferences globally.

Dr Jyotirmay Biswas is an ophthalmologist who has specialized in uveitis and ophthalmic pathology. He has done MBBS from Medical College, Calcutta and post graduation in ophthalmology from PGIMER, Chandigarh, fellowship in vitreoretinal surgery from Sankara Nethralaya. His current area of research is ocular tuberculosis, AIDS and Eales’ disease.

Dr Waduthantri Samanthila has done MBBS from China and did fellowship in uveitis from SNEC, Singapore. She is currently a Clinical research Fellow in Singapore Eye Research Institute, Singapore.
CSL Partners US Agency on Key Study to Prevent Common Causes of Abnormalities in Newborns

CSL Limited announced recently that it is partnering with the world’s largest health research agency, the US National Institutes of Health (NIH), to study a potential new treatment for the prevention of congenital CMV infection, one of the most common known causes of congenital (i.e., present at birth) abnormalities in the developed world.

Cytomegalovirus (CMV) is a common virus present in saliva, urine, tears, blood and mucus, and is predominantly carried by healthy infants, preschoolers, and children who contract the virus from their peers. Approximately one to two percent of pregnant women are infected with CMV for the first time during their pregnancy, and one in three will pass the CMV infection on to their developing unborn child. The risk of CMV infection is reduced by hand washing and general hygiene.

In Australia, CMV is one of the leading causes of disabilities in infants, including deafness, blindness, cerebral palsy, mental and physical disabilities, seizures, and even death. The symptoms of CMV may not be immediately apparent at birth, and even well beyond. There is currently no proven therapeutic prevention for congenital CMV.

The NIH will initiate a large multi-site clinical trial in the US involving more than 150,000 women to test whether CMV immunoglobulin (antibodies collected from human plasma) is an effective preventative of mother to baby transmission of CMV.

CSL is donating product made at its Swiss plant to the NIH for use in this trial as part of its commitment to addressing significant public health issues through collaborative research.

Professor Bill Rawlinson, Senior Medical Virologist at UNSW and CMV expert welcomed the study: “Robust information about prevention of congenital CMV is needed now. One to two babies are born every day with profound medical problems from congenital CMV that might be able to be prevented.”

“The commitment by the NIH and CSL to conduct a large study like this will hopefully provide more definitive answers and options for the prevention of mother to baby transmission of CMV.”

Dr Andrew Cuthbertson, Chief Scientific Officer of CSL added: “This is a very large, complex and long-term trial that requires the resources of a research agency like the NIH. CSL is very pleased to be able to support this important research, which could ultimately improve pre-natal care around the world.”

Mother of four children, including twins born with congenital CMV in 2010, Kate Daly was unaware of CMV during her pregnancy but is now very much aware of its impact. Her son William is profoundly deaf and has a significant developmental delay due to congenital CMV. His twin Emmaline has a mild developmental delay due to the virus.

“It is great to see an Australian company supporting important research in the area of CMV infection during pregnancy. Women also need to be better educated on steps they can take to avoid contracting the infection themselves, in the first place.”
China Sky One Medical to Jointly Launch Adult Stem Cell Research Enterprise

China Sky One Medical, Inc. ("China Sky One Medical" or "the Company") (NASDAQ: CSKI), a leading fully integrated pharmaceutical company in the People's Republic of China ("PRC"), announced that its wholly-owned subsidiary, Harbin Tian Di Ren Medical Science and Technology Company ("TDR"), signed an agreement (the "Agreement") to jointly set up a new company, Harbin Tian Xin Biological Engineering Ltd.

Harbin Tian Xin Biological Engineering Ltd. is being organized to perform the storage of umbilical cord stem cells. It is also to perform the clinical applications of bone marrow stem cells, intercord mesenchymal stem cells and other human stem cells.

"As we have been involved in this area of research for the past several years, we are optimistic as to the potential of the stem cell storage and application sector. We are pleased to attract outside investors to this new venture to strengthen our capability in terms of technology and capital," commented Mr. Yan-Qing Liu, Chairman and CEO of China Sky One Medical. "We expect that Harbin Tian Xin Biological Engineering Ltd. will be formally put into operation in the first quarter of 2012 and new products and services might be introduced into the market as early as year-end 2012." Mr. Liu added.

On December, 12, 2011, TDR entered into an Agreement with three parties, the No. Four Hospital Associated with Harbin Medical Science University, Harbin Zheng Yuan Construction Group and Mr. Xiao-wei Zhang, pursuant to which they will jointly set up the new company for a total capital commitment of RMB 230.0 million (approximately around $36.3 million). TDR shall invest RMB 90.0 (approximately around $14.2 million) for an ownership stake of 39%. The four parties agreed in the Agreement that 65% of the committed capital is payable within 15 days upon execution of the Agreement, and the remaining 35% is payable within six months after initial payment is made. In addition, TDR shall have the right to appoint Harbin Tian Xin's Chairman and General Manager.

China Botanic Announces Development of New Siberian Ginseng Polysaccharide Extract Powder

China Botanic Pharmaceutical Inc. (NYSE AMEX: CBP) ("China Botanic" or the "Company"), a developer, manufacturer and distributor of botanical products, bio-pharmaceuticals and traditional Chinese medicines ("TCM") in China, has announced that the Company has successfully developed a new Siberian Ginseng (Acanthopanax) Polysaccharide Extract Powder ("Extract Powder") and was also awarded the Scientific and Technological Achievements Appraisal Certificate ("Appraisal Certificate") by the Science and Technology Bureau of Heilongjiang Province.

The Siberian Ginseng (Acanthopanax) Polysaccharide Extract Powder is an all-natural substance extracted from the stem of Siberian Ginseng utilizing proprietary extraction technology developed by the China Botanic research team. The Company's Extract Powder technology was developed using its patented process of separating and extracting effective parts of the Siberian Ginseng (China Patent Number: ZL200710301682X), which was granted by the State Intellectual Property Office of the People's Republic of China in June 2011.

According to pharmacological research, Siberian Ginseng Extract Powder contains strong immunogenic and antitumor properties with minimal side effects. The Company's management estimates a significant market potential for Extract Powder based products, such as Siberian Ginseng Polysaccharide Extract Powder tablets and capsules. The Company plans to gradually launch its Extract Powder products in the market in 2012.

"We are pleased with efforts of our research and development team in developing the Acanthopanax Polysaccharide Extract Powder technology, which enables us to strengthen our market position as a leading supplier of Siberian Ginseng based products. We are confident in our ability to deliver high-quality Extract Powder products and are excited about the market opportunity in this category," commented Mr. Shaoming Li, Chairman and Chief Executive Officer of China Botanic. "The successful development of Extract Powder technology marks an important achievement for China Botanic and we believe these new Siberian Ginseng products will make a valuable contribution to our revenue growth and profitability in the future."
Merck Establishes New MSD R&D Asia Headquarters

Merck & Co., Inc., (NYSE:MRK), known as MSD outside the United States and Canada, has announced the establishment of an Asia Research & Development (R&D) headquarters for innovative drug discovery and development located in Beijing, China. The new facility is part of a $1.5 billion commitment the company has made to invest in R&D in China over the next five years.

“The establishment of the MSD Asia R&D headquarters represents an important milestone as we implement our strategy of building capabilities, and relationships to succeed in fast growing geographic regions,” said Peter S. Kim, Ph.D., president, Merck Research Laboratories. “By strategically locating in China, we are able to complement our existing R&D capabilities, and facilitate new collaborations with scientists in the region and across emerging markets.”

Located in Wangjing Park, one of Beijing’s rapidly expanding science and technology parks, the facility will consist of 47,000 square meters of office and laboratory space. The first phase of construction, scheduled to be completed by 2014, will provide capacity for approximately 600 employees working in the areas of drug discovery, translational research, clinical development, regulatory affairs and external scientific research programs.

“Merck MSD has a proud legacy of translating scientific breakthroughs into novel medicines and vaccines with proven ability to impact global human health,” said Michel Vounatsos, chairman and president, MSD in China. “We are immensely proud of the impact that MSD’s medicines and vaccines have had on improving health for the people of China as we have grown our business here, and are we eager to build on this legacy by directly investing in R&D here in China to bring forward more innovations that can help people in China and around the world.”

Merck conducts research in a broad range of therapeutic categories including cardiovascular disease and diabetes, which are becoming increasingly prevalent in China. The company’s global scientific strategy is focused on retaining deep internal therapeutic area and functional expertise in core therapeutic areas while strategically collaborating to access external innovation. Merck also maintains its commercial headquarters for MSD in China in Shanghai and has manufacturing capabilities at other locations throughout China.

Nuclear Health, GE Healthcare Join Hands in Fight against Cancer

Nuclear Healthcare Ltd (NHL), a division of Thyrocare Group, and GE Healthcare have announced a strategic partnership to establish a network of 120 molecular imaging centres to address the rapid growth of cancer incidence in India. These molecular imaging centres equipped with 120 advanced GE Discovery PET/CT imaging systems and 12 GE PET Trace Medical Cyclotrons that will produce glucose (FDG) to aid the early detection. GE Healthcare & NHL expects to establish the whole network of 120 centres by 2015 in 3 phases, a press release in Chennai said.

Cancer is one of the leading causes of death in India, with about 2.5 million cancer patients, 1 million added every year with a chance of rising five-fold by 2025 prompting Indian Council of Medical Research (ICMR) urging the Government of India to make cancer a notifiable disease. Cancer can be treated and controlled if detected early – in Stage I or Stage II. However, over 70% of cancer is detected late at a very late stage in India, when treatment is less effective and costly. While low awareness is one significant reason, unavailability of early cancer detection facilities and availability of experts is the other significant reason.

“We’re taking the fight to cancer, and reverse the trend of late detection of this dreaded disease when treatment is not effective. We pioneered advanced medical technology like molecular imaging that helps doctors diagnose early and treat cancer on a molecular level,” said Terri Bresenham, President & CEO, GE Healthcare India.

“Most people know about cancer, but don’t understand how preventable many cancers are. The answer to cancer is in creating a network of affordable early detection and treatment centres”. Said Dr A Velumani, Founder & Managing Director of Nuclear Healthcare Ltd (NHL) Mumbai.

“Our vision is to provide early cancer detection and treatment facilities in every small town in India, keeping in tradition with the innovative service facilities Thyrocare has been offering to households over the past 10 years. We are pleased to join hands with GE Healthcare provide this solid answer to cancer” he added.
Abbott and Reata Pharmaceuticals Announce Agreement to Develop and Commercialize Next-Generation Antioxidant Inflammation Modulators

Abbott and Reata Pharmaceuticals have announced that they have entered into a worldwide collaboration to jointly develop and commercialize Reata’s portfolio of second-generation oral antioxidant inflammation modulators (AIMs). The agreement is in addition to the partnership between the two companies announced in September 2010 in which Reata granted to Abbott exclusive rights to develop and commercialize its lead AIM compound, bardoxolone methyl, outside of the United States, excluding certain Asian markets.

The collaboration announced today is a global agreement and includes a large number of molecules in a broad range of therapeutic areas, including pulmonary, central nervous system disorders and immunology. Abbott and Reata will equally share costs and profits for all new AIMs in all newly licensed indications except for rheumatoid arthritis and select other autoimmune diseases, in which Abbott will take 70 percent of costs and profits and Reata will take 30 percent. The deal also includes a research agreement in which the companies will work together to discover new molecules that exhibit the same pharmacology as the AIMs already in Reata’s pipeline.

Abbott will make a one-time license payment of $400 million to Reata. The companies expect the first compound in this collaboration to enter into human clinical trials in 2012.

“We are excited to work with Abbott to develop this promising class of compounds,” Reata CEO Warren Huff said. “This deal helps Reata advance new molecules into clinical development in multiple important diseases and enables our company to build a global commercial presence.”

AIMs are potent activators of the transcription factor Nrf2. Activation of Nrf2 promotes the production of a wide range of antioxidant, detoxification, and anti-inflammatory genes. Activation of Nrf2 also inhibits NF-κB, a transcription factor that regulates many pro-inflammatory enzymes. Suppression of Nrf2 and activation of NF-κB have been associated with numerous chronic diseases, including multiple sclerosis, rheumatoid arthritis, chronic kidney disease, neurodegenerative disease and COPD. Therefore, agents that activate Nrf2 and inhibit NF-κB may be beneficial in the treatment of these chronic diseases.

“This partnership allows Abbott to enhance its promising research pipeline across multiple therapeutic areas,” said John Leonard, M.D., senior vice president, pharmaceuticals, research and development, Abbott. “Accumulating data has established the potential for antioxidant inflammation modulators in neuroscience and immunology, and we look forward to expanding our knowledge through further research.”

Under an agreement reached in September 2010, Reata granted to Abbott exclusive rights to develop and commercialize its lead AIM compound, bardoxolone methyl, outside of the United States, excluding certain Asian markets. Reata retains U.S. development and commercialization rights. Reata and Abbott are currently conducting the BEACON study, a multi-national Phase 3 clinical trial of bardoxolone methyl in patients with stage 4 chronic kidney disease and type 2 diabetes.
Lancaster Laboratories Collaborates with BioAzure

U.S.-based Lancaster Laboratories, a Eurofins Scientific company recently collaborated with Mumbai-based BioAzure Technologies 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 commercialisation while ensuring regulatory compliance, cost effectiveness, and achievement of timelines. The company provides an unmatched breadth of good manufacturing practises (GMP) and good laboratory practices (GLP) services, including protein characterisation, 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 is looking forward to work closely with BioAzure to enable Indian biotech companies to achieve their regulatory compliance objectives for their product development and manufacturing activities,” said Timothy S Oostdyk, president, Lancaster Laboratories.

He added, “With the goal of delivering a seamless service experience, we plan to focus on ways to customise 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 said, “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.”

BioAzure works with the therapeutic biotechnology industry in India to enable its clients to obtain quicker, more cost-efficient and regulatory compliant results from their biotechnology development and manufacturing programs through BioAzure’s relationships with global companies.

Samsung and Biogen Idec Announce Joint Venture to Develop, Manufacture and Market Biosimilars

Samsung and Biogen Idec (NASDAQ: BIIB) have announced that they have entered into an agreement to invest $300 million to establish a joint venture to develop, manufacture and market biosimilars. Samsung will take a leading role in the joint venture, with Biogen Idec contributing its expertise in protein engineering and biologics manufacturing.

Under the terms of the agreement, Samsung will contribute $255 million of the $300 million for an 85 percent stake and Biogen Idec will contribute $45 million for a 15 percent stake in the joint venture. The joint venture, which will be based in Korea, will contract with Biogen Idec and Samsung Biologics for technical development and manufacturing services. Samsung Biologics is a Samsung business formed in April 2011 to specialize in biopharmaceutical manufacturing. The joint venture will not pursue biosimilars of Biogen Idec’s proprietary products.

“At Samsung, one of our goals is to help patients around the world by increasing the accessibility and affordability of existing medicines,” said Tae-Han Kim, Ph.D., CEO of Samsung Biologics. “Since many of the world’s top-selling drugs are biologics, developing and making high-quality biosimilars is critical to that goal. By combining Biogen Idec’s expertise in biologics with our business acumen and proven record of success in new business development, we are taking a significant step toward becoming a major player in the biopharmaceutical industry and investing in an important growth engine for our company.”

“The future of healthcare will continue to be driven by innovation, but it will also be about ensuring patients have access to cost-effective therapies, and biosimilars will play an important role in that,” said George A. Scangos, Ph.D., CEO of Biogen Idec. “This relationship will allow us to leverage our world-class protein engineering and biologics manufacturing capabilities, while maintaining focus on our mission of discovering, developing and delivering innovative therapies for patients worldwide with neurodegenerative diseases, hemophilia and autoimmune disorders. We are very impressed with Samsung’s track record of leadership and excellence in all their businesses and are excited to be working with them.”

Completion of the transaction is subject to customary closing conditions, including antitrust clearance by the U.S. and Korean regulators.
Agilent Technologies and Monash University Sunway Campus Boost Talent and Skills for Genomics Research in Malaysia

Agilent Technologies Inc. (NYSE: A) and Monash University Sunway campus have announced a collaboration to promote talent and skills development for genomics research in Malaysia.

This partnership, the first of its kind for Agilent with a university in Malaysia, will help Malaysia assert itself as a leading center for life sciences research and development in Southeast Asia. Under the agreement, a center of excellence known as the Monash-Agilent Authorized Microarray Service Center will be established at Monash University Sunway campus. This center will be equipped with the latest microarray instruments and will provide competency training for the center’s lab professionals undertaking molecular-genetic studies of human disease.

"The establishment of the AMSC will be a timely boost in the collaboration between Agilent and Monash University Sunway campus through the Jeffrey Cheah School of Medicine and Health Sciences, providing the opportunity to access advanced technologies to strengthen our current genomics research in diabetes, cancer, neurobiology and infectious diseases," said Professor Dato' Dr Anuar Zaini Md Zain, Head of the school.

He added that the school has forged strong collaborations with local and international academic institutions as well as leading industry players in expanding its expertise in research.

The collaboration between Agilent and Monash University Sunway campus will see knowledge-sharing between both organizations, including real-time communication of new developments in the field of microarray applications as well as networking with Agilent’s global customers who are shaping the future of genomics.

Genomics is the study of all genes of an organism, and DNA microarrays enable the measurement of multiple molecular changes to genes. These changes can reveal the molecular basis of diseases, enabling scientists to discover and develop new methods of treatment for these diseases.

"The Monash-Agilent Authorized Microarray Service Center, together with existing platform technologies at the school, such as liquid chromatography/mass spectrometry and proteomics, will encourage integrative and multidisciplinary research. The center will become the platform to train next-generation scientists in genomics research and potentially spearhead new niche areas in biomedical research through support and networking with Agilent’s global customers/collaborators," said professor Anuar.

“We are excited about this collaboration with Monash University Sunway campus,” said Rod Minett, general manager, Agilent Life Sciences Group, South Asia Pacific and Korea. “The knowledge gleaned from the collaboration will not only contribute toward further understanding and preventing diseases, but also cement Malaysia as a center for life sciences research and development.”

At the heart of this collaboration are highly sensitive and flexible DNA microarrays and the instruments and software to interpret them. DNA microarrays are manufactured by Agilent using the same cutting-edge technology used in ink-jet printer nozzles to literally synthesize new DNA strands directly on a glass surface. Then these strands (or probes) are used in experiments to detect changes in the DNA such as gene copy number variations, or to monitor gene expression levels under various conditions. Agilent’s SureScan microarray scanner provides the means to read information from these microarrays, enabling scientists and laboratory professionals in the new center to leverage the latest tools for understanding the molecular-genetic basis of disease.
**S*BIO’s Novel JAK2 Inhibitor Pacritinib (SB1518) Effectively Reduces Splenomegaly in Myelofibrosis (MF) Patients**

*S*BIO Pte Ltd has announced that results from a Phase 2 study demonstrated that its JAK2 inhibitor pacritinib (SB1518) effectively reduced splenomegaly in myelofibrosis (MF) patients, with minimal impact on existing cytopenias providing an important therapeutic niche in the treatment of MF. Results were presented at the 53rd ASH Annual Meeting and Exposition in San Diego.

“Pacritinib is an active drug for the treatment of splenomegaly in patients with primary myelofibrosis, post-polycythemia vera-myelofibrosis and post-essential thrombocytopenia-myelofibrosis regardless of baseline thrombocytopenia,” said Rami S. Komrokji, M.D., principal author of the oral presentation. “The once daily dose of pacritinib was well tolerated with manageable gastrointestinal toxicity as the main side effect. The minimal impact on existing cytopenias in MF patients provides an important therapeutic outcome for pacritinib in the treatment of this patient population. The results support the rapid advancement of pacritinib into Phase 3 clinical trials to further support its safety and efficacy.”

The primary endpoint of pacritinib’s Phase 2 study was to assess the spleen response rate, defined as a >/=35% reduction in MRI-measured spleen volume between baseline and week 24. Thirty-four MF patients were enrolled in the study. The most common treatment-related adverse events were gastrointestinal, which were generally low grade and easily managed. Pacritinib was equally well tolerated by patients with normal platelet counts and those with thrombocytopenia and anemia. Thirty patients (88%) showed reduction in palpable splenomegaly, 14 (41%) showed decreases of >/=50% and five (15%) achieved clinical resolution of splenomegaly. Eight patients (24%) had decreases in spleen volume by >/=35%. Spleen response rates were equivalent among patients with low baseline platelet counts and those with normal baseline counts. At the six-month visit, a significant reduction (>2 point improvement in mean symptom score) was observed for MF-associated symptoms, including abdominal pain, bone pain, early satiety, worst fatigue, inactivity, night sweats and pruritus.

“There is a significant medical need in the treatment of myelofibrosis and the results from pacritinib’s clinical trials encourage us to quickly move forward with a global Phase 3 study to further demonstrate pacritinib’s clinical benefits and consequently capture an important niche market in the treatment of MF,” said Tamar Howson, interim CEO and board member of S*BIO.

Pacritinib is a small molecule JAK2-selective kinase inhibitor, which has demonstrated high potency in preclinical models against both the wild type JAK2 kinase and the JAK2 kinase with the V617F mutation. The V617F mutation is found in high frequencies in myeloproliferative disorders such as MF. It is estimated that approximately 50% of patients with MF possess the JAK2 mutation.
A new study has found a link between increases in body temperature and the incidence of stillbirth and even shorter pregnancies.

An international team, led by the Queensland University of Technology, looked at the incidence of still and premature births in Brisbane over a four-year period from 2005, American Journal of Epidemiology reported.

Professor Adrian Barnett, who led the team, said a total of 101,870 births were recorded throughout the period and of these 653 were stillbirths. “We found that increases in temperature increased the risk of stillbirth, and this was particularly true in the earlier stages of pregnancy before 28 weeks. Our estimated numbers were at 15°C there would be 353 stillbirths per 100,000 pregnancies, as compared with 610 stillbirths per 100,000 pregnancies at 23 degree Celsius. "Increased temperatures also shortened gestation times, which means more preterm babies who often have serious long-term health problems such as cerebral palsy and impaired vision and hearing," he said.

The study recorded weekly temperature, humidity and air pollution levels for each pregnancy. Prof Barnett said that the lowest risks were in the coolest weeks, and that warm temperatures with weekly means of 23°C were just as dangerous as the hottest weeks. “This could be because most pregnant women would be more conscious of trying to remain cool on the hottest days and would generally seek air conditioning,” he said.

Prof Barnett said as global temperatures rise, the study could have serious public health implications. “Pregnant women should protect themselves from overheating to reduce the likelihood of pre-term or stillbirths,” he said. He added: “Stillbirths are obviously devastating for families, and many stillbirths have an unknown cause so more research is needed to help prevent them. “It is known that women should avoid hot tubs or Jacuzzis during pregnancy as this can cause a pregnancy termination, and that dehydration caused by heat stress and sweating could be harmful to a foetus and induce birth.”
GIS Researchers Develop Systematic Method for Accurate DNA Sequence Reconstruction

Researchers at the Genome Institute of Singapore (GIS) have, for the very first time, developed a computational tool that comes with a guarantee on its reliability when reconstructing the DNA sequence of organisms, thus enabling a more streamlined process for reconstructing and studying genomic sequences.

The work, lead by Dr Niranjan Nagarajan, Assistant Director of Computational and Mathematical Biology at the GIS, was reported in the November 2011 issue of the Journal of Computational Biology.

The genomic study of life (plants and animals alike) is based on computational tools that can first piece together the DNA sequence of these organisms, a process called genome assembly, that is similar to solving a giant puzzle or putting together the words in a book from a shredded copy. Due to the sheer scale of this challenge, existing approaches for genome assembly rely on heuristics and often result in incorrect reconstructions of the genome. The work reported here represents the first algorithmic solution for genome assembly that provides a quality guarantee and scales to large datasets. A new and improved implementation for this algorithm called Opera is now freely available at http://sourceforge.net/projects/operasf/ and has been used at the GIS for successfully assembling large plant and animal genomes.

The assembled genome of an organism forms the basis for a range of downstream biological investigations and serves as a critical resource for the research community. The draft human genome, for example, was obtained at the expense of billions of dollars, serves as a fundamental resource for biomedical research and is, in fact, still being refined. Improved assembly tools thus serve to generate the most complete and accurate draft genomes that can be reconstructed from the data, avoiding mis-assembly related dead-ends for downstream research as well as minimizing the painstaking effort needed to refine and correct a draft assembly.

"Genetic studies of organisms of interest for human health (such as those causing infectious diseases), agriculture, animal husbandry and other areas of the bio-economy, such as biofuels, are driven by the availability of draft genome sequences, said Dr Nagarajan. "This research describes a novel computational approach to reconstruct more complete and accurate draft genomes. From an algorithmic perspective, Opera demonstrates the utility of a clear optimization function and an exact algorithm derived from a parametric complexity analysis in providing a robust solution to a seemingly intractable problem."

Mihai Pop, Associate Prof, Department of Computer Science; and Interim Director, Center for Bioinformatics and Computational Biology at the University of Maryland said: "Opera is an important advance in genome assembly algorithms – currently it is the best stand-alone genome scaffolder available in the community. In Opera, Dr Nagarajan's team has introduced a rigorous theoretical framework for genome scaffolding as well as a practical implementation that achieves remarkable performance. These results are impressive given the substantial research in the field over the past 30 years, as well as the numerous developments spurred in recent years by advances in sequencing technologies."
A research team led by Dr John Yu, distinguished research fellow at the Institute of Cellular and Organismic Biology (ICOB), Academia Sinica, Taiwan, has discovered that glycosphingolipids on the surface of cells change composition when human embryonic stem cells differentiate into precursors of specialized cells such as neurons, or liver and pancreas cells. This finding contributes to the search for safe ways of using stem cells for regenerative medicine.

Regeneration of damaged tissues is one of the holy grails in medical research, and embryonic stem cells, with their ability to renew themselves and differentiate into a diverse range of specialized cell-types, are considered a promising source for cell replacement therapies. Unfortunately, alongside their differentiation ability, embryonic stem cells also have a propensity to develop into tumors, a characteristic that currently presents a large obstacle to their clinical use.

The team of researchers from the ICOB, Genomics Research Center (GRC) and Institute of Biological Chemistry recently discovered that a type of compounds found on the surface of human embryonic stem cells, called glycosphingolipids, change composition as the cells differentiate into precursors of specialized cells such as neurons and liver cells. These findings suggest that glycosphingolipids might be suitable for use as markers of the state of differentiation of stem cells. A knowledge of the state of differentiation of these cells may allow researchers to develop a method by which to sort undifferentiated cells from those that are differentiated, and thus, perhaps allow removal of the undifferentiated cells most likely to form tumors bringing the safe regeneration of human cells or organs one step closer.

The team, including Dr Chia-Ning Shen, assistant research fellow at the GRC, and Dr Kay-Hooi Khoo, an adjunct research fellow at the GRC, studied the compounds using matrix assisted laser desorption ionisation (MALDI) MS mass spectrometry technology. They found that during differentiation into neural progenitor cells, the core structures of glycosphingolipids on human embryonic stem cells switched mostly to the ganglio-series type. On the other hand, when human embryonic stem cells differentiated into endodermal cells (precursors of liver and pancreas cells), the prominent glycosphingolipid identified was Gb4Cer.

Dr Yu, who is also an adjunct distinguished research fellow at the GRC, said he hoped the advance will pave the way for developing new strategies for safer stem cell-based therapies in regenerative medicine.
# JANUARY 2012

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<tr>
<td>27 – 29 January</td>
<td>38th National Annual Conference of the Indian Association of Clinical Psychologists</td>
<td>Pune, Maharashtra</td>
<td><a href="mailto:iacp2012@cccpune.com">iacp2012@cccpune.com</a></td>
<td><a href="http://iacp.krishagni.com/">http://iacp.krishagni.com/</a></td>
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# FEBRUARY 2012

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<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Location</th>
<th>Contact Person</th>
<th>Email/Phone</th>
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<tr>
<td>2 – 5 February</td>
<td>70th All India Ophthalmological Society Annual Conference</td>
<td>New Delhi, India</td>
<td><a href="mailto:aioc2012@gmail.com">aioc2012@gmail.com</a></td>
<td><a href="http://www.aios.org/annualconf.asp">http://www.aios.org/annualconf.asp</a></td>
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<tr>
<td>3 – 5 February</td>
<td>3rd International Conference on Current Trends in Forensic Sciences, Forensic Medicine &amp; Toxicology</td>
<td>Jaipur, India</td>
<td><a href="mailto:rksharman@iitd.ernet">rksharman@iitd.ernet</a></td>
<td><a href="http://www.samcon.org/home/">http://www.samcon.org/home/</a></td>
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<tr>
<td>9 – 11 February</td>
<td>EMS 2012 - International Congress on Emergency Medical Service Systems</td>
<td>New Delhi, India</td>
<td><a href="mailto:info@ems2012.in">info@ems2012.in</a></td>
<td><a href="http://www.aesociety.org/">http://www.aesociety.org/</a></td>
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<tr>
<td>9 – 11 February</td>
<td>BioAsia 2012</td>
<td>Hyderabad, India</td>
<td><a href="mailto:info@bioasia.in">info@bioasia.in</a></td>
<td><a href="http://www.bioasia.in/2012/">http://www.bioasia.in/2012/</a></td>
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<tr>
<td>11 – 12 February</td>
<td>1st Asia Pacific Breast Cancer Summit</td>
<td>Singapore</td>
<td><a href="mailto:abc@abc.com">abc@abc.com</a></td>
<td><a href="http://abcs2012.org/index.php">http://abcs2012.org/index.php</a></td>
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<tr>
<td>20 – 23 February</td>
<td>Antibodies Asia</td>
<td>Shanghai, China</td>
<td><a href="mailto:register@ibcasia.com.sg">register@ibcasia.com.sg</a></td>
<td><a href="http://www.antibodiesasia.com">http://www.antibodiesasia.com</a></td>
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<tr>
<td>20 – 23 February</td>
<td>Cell Line Development and Engineering Asia</td>
<td>Shanghai, China</td>
<td><a href="mailto:register@ibcasia.com.sg">register@ibcasia.com.sg</a></td>
<td><a href="http://www.celllineasia.com">http://www.celllineasia.com</a></td>
<td></td>
</tr>
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</table>
MARCH 2012

3 – 4 March
NYSORA Asia 2012
Vietnam
Contact Person: Mr Yap Hong Yi
Tel: +65 6778 5620
Fax: +65 6778 1372
Email: na2012@pinghealthcare.com
URL: http://www.NYSORAsia.com/

8 – 11 March
20th Annual Meeting of the Asian Society for Cardiotoracic Surgery
Bali, Indonesia
Contact Person: Latifa Hernisa
Tel: +1162 21566 5993
Fax: +1162 21 566 5993
Email: info@ascvtsbali2012.org
URL: www.ascvtsbali2012.org/

13 – 15 March
Innovations in Healthcare Management and Informatics
Bangkok, Thailand
Contact: Samuel Seah
Tel: +65 6722 8388
Email: enquiry@iqpc.com.sg

19 – 22 March
1st World Congress on Healthy Ageing 2012
Kuala Lumpur, Malaysia
Tel: +11 3 2070 5600
Email: jclim@dynamicmerit.com
URL: www.healthageingcongress.com/

19 – 22 March
5th annual BioPharma Asia Convention 2012
Marina Bay Sands, Singapore
Contact: Valerie Lim
Tel: +65 6322 2766
Email: valerie.lim@terrapinn.com
URL: http://www.terrapinn.com/exhibition/biopharma-asia

APRIL 2012

12 – 15 April
4th Spring Meeting of the International Society for Dermatologic Surgery (ISDS)
Tel: +1149 6151 951 8892
Fax: +1149 6151 951 8893
URL: www.isdsworld.com/en/upcoming-congresses

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/

MAY 2012

4 – 6 May
World Congress on Biotechnology
Hyderabad, Andhra Pradesh, India
Contact Person: Hari Krishnan
URL: www.brightice.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
<mailto:general@coastal.com.hk>
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