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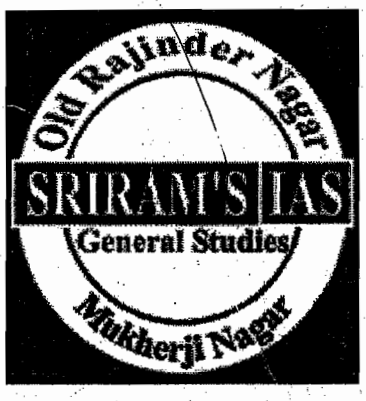

GENERAL STUDIES

Additional topics in Sc.&Tech (paper-III)

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Stem cells

induced pluripotent stem cells

Introduction

During embryonic development, specialized cells (e.g., muscle or immune cells) arise from a common stem cell that differentiates via a series of cellular changes triggered by specific gene expression patterns. Scientists can recover these embryonic stem (ES) cells from embryos and manipulate them in vitro to study early development. They can also differentiate ES cells into cell types that are useful for therapeutic purposes, such as transplantation. This technology raises a significant ethical concern because most ES cells arise from human embryos. Some ethical concerns may be circumvented by the discovery that somatic cells can be reprogrammed to a pluripotent state. The reprogrammed cells, called induced pluripotent stem (iPS) cells, exhibit functional similarities to ES cells and present an exciting area of research. The ability to reprogram somatic cells into iPS cells that are pluripotent and can self-renew has transformed the fields of developmental biology and regenerative medicine.

Reprogramming Somatic Cells into Pluripotent iPS Cells

Earlier experiments in cell fusion and nuclear transfer showed that gene expression in differentiated cells remained dynamic and reversible. Silent genes in a specific cell type can be reactivated by fusing the cells with a different cell type. Subsequently, several studies showed that introduction of defined transcription factors could convert specialized cell types from one lineage to another. When somatic cells were reprogrammed by transferring their nuclei into oocytes or by fusion with ES cells, genome-wide transcriptional activity and DNA methylation patterns were converted from the somatic state to an embryonic state.

In 2006, Kazutoshi Takahashi and Shinya Yamanaka established for the first time murine ES-like cell lines from mouse embryonic fibroblasts (MEFs) and skin fibroblasts by simply expressing four transcription factor genes encoding Oct4, Sox2, Klf4, and c-Myc (Takahashi & Yamanaka 2006). They called these somatic cell-derived cell lines induced pluripotent stem (iPS) cells. These iPS cell lines exhibit similar morphology and growth properties as ES cells and express ES cell-specific genes. Transplantation of iPS cells into immunodeficient mice resulted in the formation of germ-cell-tumor (teratoma)-containing tissues from all three germ layers, confirming the pluripotent potential of iPS cells. However, there were two problems: the low efficiency of establishing iPS cell lines and some variations in gene expression profiling between iPS cells and ES cells. The latter issue raised the concern that cell reprogramming may be insufficient to restore full pluripotency in somatic cells as exhibited by ES cells.

Tetraploid blastocyst complementation assay

The most stringent test for pluripotency is known as the tetraploid blastocyst complementation assay. The method involves merging the embryonic (ES or iPS cells) and extraembryonic tissue (tetraploid cells) from two different species of animals and then testing to see if the embryonic tissue is sufficient for the normal development to the adult stage. Using this assay, several studies now show the production of fertile adult mice derived entirely from iPS cells, therefore confirming the true pluripotency gained by iPS cells during the reprogramming process.

Modeling Human Diseases with iPS Cells

Availability of patient-specific iPS cell lines provides unprecedented opportunities to elucidate disease mechanisms in vitro, to carry out drug screening and toxicology studies, and

to advance cell replacement therapy in regenerative medicine (Colman & Dreesen 2009). Reprogramming of fibroblasts from patients with Mendelian and complex genetic disorders — such as amyotrophic lateral sclerosis, type 1 diabetes, Parkinson's disease, and Duchenne muscular dystrophy — allows the establishment of disease-specific iPS cell lines. To study the disease mechanism, a key issue is whether the affected cell type derived from iPS cells can recapitulate the disease phenotype.

However, the use of iPS cells to model adult-onset diseases such as Parkinson's disease and amyotrophic lateral sclerosis proves to be more elusive. Relevant cell types derived from patients' iPS cells of these diseases have so far failed to exhibit disease-related phenotypes. Exposure of the differentiating cells to stress conditions by increasing the level of nitrogen and oxygen reactive species, proinflammatory factors, or even toxins may be necessary to speed up the emergence of pathological status in relevant cell types derived from iPS cells.

The other limitation in modeling human diseases with iPS cells is that a single cell type may not be sufficient to manifest the full spectrum of pathogenesis. Interaction among different cell types may be important to reconstruct the disease phenotypes faithfully. In this case, we first need to identify the interacting cell types and then work out a protocol for iPS cell differentiation into these cell types so as to recapitulate full disease phenotypes. Ultimately, it may be necessary to transplant iPS-derived cells into immunodeficient mice to reveal disease phenotypes.

The Limitations of Reprogrammed iPS Cells

The most noted problem is the use of retroviral and lentiviral vectors to introduce the four transcription factor genes into somatic cells for cell reprogramming. These viral vectors preferentially integrate into active genes and therefore have the potential to activate flanking cellular genes and transform the transplanted cells. In addition, most of the four introduced transcription factors possess oncogenic potentials, and persistent expression of any of them may provide cell growth advantage and increase the chance for cell transformation. Although expression of these four genes for the most part is silent in established iPS cell lines, residual expression or reactivation of their expression in transplanted iPS cells can induce tumors in mice. Thus, although iPS cells derived from this route may be suitable for the study of disease mechanisms or for drug screening and validation, they definitely are not suitable for cell replacement therapy.

Many alternative gene delivery strategies — including the use of episomal vectors, nonintegrating viral vectors, transient DNA transfection, transposons, and protein transduction — can overcome this problem. A general principle common to all these strategies is the transient expression of the four transcription factors at sufficient levels to trigger the initiation of the cell reprogramming event without permanent integration of the four genes into the host genome. Although these strategies work for the most part, the efficiency of generating iPS cell lines is significantly reduced compared with the approach of retroviral and lentiviral vectors.

Use of small molecules to activate the pluripotency program in somatic cells represents perhaps the safest approach to create reprogramming factor-free iPS cells. Several small molecules, when used singly, could substitute for some of the reprogramming factors. However, so far it is not possible to use only small molecules to reprogram somatic cells. High throughput screening of small molecules for cell reprogramming is ongoing in many laboratories, and the ultimate goal would be to establish iPS cells free of any exogenously introduced DNA fragments.

Yet another problem with iPS cells in the study of disease mechanism is that defining a disease-related phenotype is frequently hindered by the intrinsic variability in differentiation potentials observed among different iPS cell lines. This variability makes it less certain that any observed phenotype in cells derived from a single iPS cell line is caused by the defective gene function. Therefore, to ensure that the exhibited phenotypes are not unique to a specific iPS cell line or a particular patient, it is important to evaluate several iPS cell lines generated from the same patient as well as those generated from different patients with the same disease. Alternatively, restoration of the missing gene function in mutant iPS cells provides an ideal isogenic control for any observed phenotype.

Clinical trial

Retinal pigment epithelial

The first human clinical trial using autologous iPSCs is approved by the Japan Ministry Health and will be conducted in 2014 in Kobe. iPSCs derived from skin cells from six patients suffering from wet age-related macular degeneration will be reprogrammed to differentiate into retinal pigment epithelial (RPE) cells. The cell sheet will be transplanted into the affected retina where the degenerated RPE tissue has been excised. Safety and vision restoration monitoring is expected to last one to three years. The benefits of using autologous iPSCs are that there is theoretically no risk of rejection and it eliminates the need to use embryonic stem cells.

Lifestyle diseases to cost India $6 trillion

The Harvard School of Public Health has, in a study on economic losses due to non-communicable diseases (NCDs), estimated that the economic burden of these ailments for India will be close to $6.2 trillion for the period 2012-30, a figure that is equivalent to nearly nine times the total health expenditure during the previous 19 years of $710 billion.

NCDs, chiefly cardiovascular diseases (including heart disease and stroke), diabetes, cancer and chronic respiratory diseases, are defined as diseases of long duration and generally slow progression. They are the major cause of adult mortality and illness worldwide.

The Harvard report, which is based on WHO projections of the mortality trajectory associated with NCDs, says ischemic heart disease is going to be the single most costly non-communicable disease in India (causing an output loss of about $1.21 trillion over 2012-30), followed by chronic obstructive pulmonary disease (COPD).

Most of the non-communicable diseases, for example diabetes or heart disease, affect the person in the productive years. They cause reduced productivity and early retirement. Also, they put immense pressure on public health expenditure as in most cases the treatment costs are higher compared to communicable diseases.

The increasing burden of NCDs could rob India of the 'demographic dividend' it is projected to reap on account of a predominantly young population. A recent report published by IRIS Knowledge Foundation in collaboration with UN-HABITAT states that by 2020, India is set to become the world's youngest country with 64% of its population in the working age group.

The WHO has suggested 'best buy' interventions (policy measures) for reducing NCDs that include increasing tax on tobacco products and alcohol and ban on their advertising. It also

proposes interventions such as reduced salt intake in food, counselling and multi-drug therapy for people with a high risk of developing heart attacks and strokes, and hepatitis B immunization to prevent liver cancer.

"The implementation of these 'best buy' interventions for reducing NCDs in low-and-middle income countries (LMICs) could lead to a 10-15 percent reduction in premature death from NCDs (and in their economic costs)," the Harvard researchers have pointed out.

An earlier study conducted by the World Economic Forum and Harvard School of Public Health estimated that a 12.5% reduction in ischemic heart disease, for example, could lead to economic savings of $25 billion per year over the period 2011-2025.

Dr Renu Garg, WHO's regional advisor of non-communicable diseases for South East Asia, said that India is going to adopt the New Delhi declaration on high blood pressure in the WHO meet to be held in the national capital next week. The declaration, a policy framework, aims to reduce hypertension, a major risk factor for NCDs like heart attack and stroke.

The New Delhi Declaration on September 10 will be followed by the 66th Session of the WHO regional committee which meets once a year to review progress and regional implications of the World Health Assembly decisions and to map the way forward. The focus areas include universal health coverage, adoption of the global targets for prevention and control of non-communicable diseases and measles and rubella control.

The targets include 10% reduction in alcohol consumption, halt in rise of obesity and diabetes and 50% reduction in households using solid fuels for household cooking.

National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular diseases and Stroke (NPCDCS) is the pilot programme that the GoI has started to tackle the growing menace of non-communicable diseases. It entails health education and mass media efforts at country level, opportunistic screening of persons above the age of 30 years, establishment of Non Communicable Disease (NCD) clinics at CHC and district level, development of trained manpower and strengthening of tertiary level health facilities.

Polypill for CVDs

For the first time, doctors and researchers have come up with a single pill for all cardiovascular diseases (CVD), including high blood pressure and vulnerability to stroke, doing away with the pain of popping multiple pills to keep your heart healthy.

In India, compliance to multiple pills for CVD is as low as 10%.

While studies have shown that patients with CVD do not take recommended medications in the long-term, the use of fixed-dose combinations (FDCs) like a polypill improves adherence to a large extent. The study showed adherence rate increasing by 20% with use of the polypill, a combination of aspirin, statin (cholesterol lowering drugs), and two blood pressure-lowering agents.

Polycap is a specific five-in-one fixed dose combination polypill created by Cadila Pharmaceuticals Limited of Ahmedabad, India that combines moderate levels of five

different medications in a single, one-a-day pill aimed at reducing/preventing heart attacks and strokes. A prominent 2009 study found that this pill's combination of three blood pressure medications, a cholesterol reducer, and aspirin had cut the risk of heart attack and stroke in half, with no more adverse effects than taking the components separately.

As tested, 'Polycap' combines 100 milligrams of aspirin, with simvastatin (a generic version of Zocor, the cholesterol-lowering statin; 20 mg) and low doses of three blood pressure medications, atenolol (50 mg), ramipril (5 mg) and thiazide (12.5 mg). And despite containing multiple drugs, the pill has a fairly small size which can facilitate swallowing.

Obesity and liver cancer

Obesity has become more prevalent in most developed countries over the past few decades, and is increasingly recognized as a major risk factor for several common types of cancer. As the worldwide obesity epidemic has shown no signs of abating, better understanding of the mechanisms underlying obesity-associated cancer is urgently needed. Although several events were proposed to be involved in obesity-associated cancer, the exact molecular mechanisms that integrate these events have remained largely unclear.

It has now been shown that senescence-associated secretory phenotype (SASP) has crucial roles in promoting obesity-associated hepatocellular carcinoma (HCC) development in mice. Dietary or genetic obesity induces alterations of gut microbiota, thereby increasing the levels of deoxycholic acid (DCA), a gut bacterial metabolite known to cause DNA damage. The enterohepatic circulation of DCA provokes SASP phenotype in hepatic stellate cells (HSCs), which in turn secretes various inflammatory and tumour-promoting factors in the liver, thus facilitating HCC development in mice after exposure to chemical carcinogen.

Notably, blocking DCA production or reducing gut bacteria efficiently prevents HCC development in obese mice. Similar results were also observed in mice lacking an SASP inducer or depleted of senescent HSCs, indicating that the DCA–SASP axis in HSCs has key roles in obesity-associated HCC development. Moreover, signs of SASP were also observed in the HSCs in the area of HCC arising in patients with non-alcoholic steatohepatitis, indicating that a similar pathway may contribute to at least certain aspects of obesity-associated HCC development in humans as well.

Plants communicate via underground fungus

Mycorrhizae are mutualistic - they both need and are needed by the plants whose roots they inhabit

Plants can communicate the onset of an attack from aphids by making use of an underground network of fungi, researchers have found.

Instances of plant communication through the air have been documented, in which chemicals emitted by a damaged plant can be picked up by a neighbour.

But below ground, most land plants are connected by fungi called mycorrhizae.

The new study, published in Ecology Letters, demonstrates clearly that these fungi also aid in communication.

It joins an established body of literature, recently reviewed in the Journal of Chemical Ecology and in Trends in Plant Science, which has suggested that the mycorrhizae can act as a kind of information network among plants.

Researchers from the University of Aberdeen, the James Hutton Institute and Rothamsted Research, all in the UK, devised a clever experiment to isolate the effects of these thread-like networks.

The team concerned themselves with aphids, tiny insects that feed on and damage plants.

Many plants have a chemical armoury that they deploy when aphids attack, with chemicals that both repel the aphids and attract parasitic wasps that are aphids' natural predators.

The team grew sets of five broad bean plants, allowing three in each group to develop mycorrhizal networks, and preventing the networks' growth in the other two.

To prevent any through-the-air chemical communication, the plants were covered with bags.

As the researchers allowed single plants in the sets to be infested with aphids, they found that if the infested plant was connected to another by the mycorrhizae, the un-infested plant began to mount its chemical defence.

Those unconnected by the networks appeared not to receive the signal of attack, and showed no chemical response.

"Mycorrhizal fungi need to get [products of photosynthesis] from the plant, and they have to do something for the plant," explained John Pickett of Rothamsted Research.

"In the past, we thought of them making nutrients available from the [roots and soil], but now we see another evolutionary role for them in which they pay the plant back by transmitting the signal efficiently," he told BBC News.

Prof Pickett expressed his "abject surprise that it was just so powerful - just such a fantastic signalling system".

The finding could be put to use in many crops that suffer aphid damage, by arranging for a particular, "sacrificial" plant to be more susceptible to aphid infestation, so that when aphids threaten, the network can provide advance notice for the rest of the crop.

"Now we've got a chance in a really robust manner of switching on the defence when it is needed - not straining the plant to do it all the time - and to reduce the development of resistance (of the aphids to the plants' defences)," Prof Pickett said.

Universal testing for HIV every five years would be cost effective for India

In India most people who are HIV positive don't know it, yet testing and treatment are relatively cheap and available. It would therefore meet international standards of cost-effectiveness — and save millions of lives for decades — to test every person in the billion-plus population every five years according to a new study published in the journal *PLoS One*.

"Testing even 800 million adults is a public health undertaking of a historic magnitude, but what we were able to show is that ... even under those dire circumstances, testing this frequently and this widely still was reasonable."

The findings are based on a careful analysis of India's HIV epidemic using the Cost-Effectiveness of Preventing AIDS Complications (CEPAC) International model, a sophisticated statistical tool that has already been used in HIV policymaking in France, South Africa, and other countries. A team of researchers at Brown, Yale, Massachusetts General Hospital, Harvard, and in Chennai, India, integrated scores of factors specific to the country to find that testing for the whole country, with greater frequency for high-risk groups and areas, would pay off despite India's huge population and even in cases where conditions are worse than the researchers assume.

"Testing even 800 million adults is a public health undertaking of a historic magnitude," said study co-lead author Dr. Kartik Venkatesh, a postdoctoral fellow at Brown University and Women & Infants Hospital. "But what we were able to show is that even if you increase the cost of HIV treatment and care pretty significantly and really decrease the number of individuals who would link to care, even under those dire circumstances, testing this frequently and this widely still was reasonable."

Co-author Dr. Soumya Swaminathan, director of the National Institute for Research in Tuberculosis in Chennai, India, said the projections of the model will help the country in its battle with the epidemic, one of the world's largest.

"The paper explores various strategies and suggests cost-effective options for HIV testing in India," Swaminathan said. "As India moves ahead in its HIV prevention activities and aims for zero new infections, expanding testing will be a key priority and this analysis should help policymakers make the best decisions."

Dollars per life-years saved

The main results from the model are projections of the dollar cost per year of extended lifespan. The World Health Organization's standard for cost effectiveness is an expenditure that is less than three times the per capita GDP of a country. In India in 2010, per capita GDP was $1,300. A program is therefore cost-effective in India if the expense is less than $3,900 to save a year of someone's life.

Modern antiretroviral therapies can give HIV-positive people a normal lifespan, and in India, which has a thriving generic pharmaceutical sector, first-line therapy costs only $8.61 a month (second-line therapy for those whose viruses prove resistant is $55.12 a month). HIV tests, meanwhile, cost only $3.33.

They ran the models not only for the general population but also for people in high-risk districts and high-risk groups (e.g., with a higher prevalence of the virus but with more frequent testing today).

As they ran the numbers to determine the costs and effects on patients of broader and more frequent testing, they compared the results to what would happen under the status quo, in which there is less-than-universal testing.

Here is what they found:

- Testing the general population just once would be "very cost-effective" because it would cost $1,100 per year of life saved (YLS) in general and $800 per YLS among high-risk populations.
- Testing the population every five years would be "cost-effective" with a price of $1,900 per YLS saved in general, and $1,300 per YLS among high-risk groups.
- Testing annually would not be cost-effective for the general population ($4,000/YLS), but would be for high-risk people ($1,800/YLS).

The general trends of cost effectiveness remained even after "sensitivity" analyses in which the researchers entered different statistical assumptions in the model in case their assumptions were too optimistic. But to make testing the general population every five years no longer cost-effective, the researchers had to tell the model that only 20 percent of the general population would agree to testing and only 20 percent of positive patients would get care.

Addressing an epidemic

Venkatesh said the main benefit of national testing would simply be getting more people to learn they are positive and therefore to seek effective care before they have full-blown AIDS and a complication. A secondary benefit, however, would be to curb transmission of the virus, both because behavior can change and because therapy can reduce transmissibility.

National AIDS Control Programme

NACP-IV seeks to consolidate the gains of NACP-III and learn from the lessons of the previous phases of programme implementation. It aspires to further strengthen and decentralize the programme to state and district levels. NACP-IV remains a prevention-oriented plan with adequate coverage of HIV care in the context of the concentrated epidemic situation in India.

Taking into account the successful implementation of NACP III and outcome of wider consultation, the salient features of NACP IV are:

· Preventing new infections by sustaining the reach of current interventions and effectively addressing emerging epidemics

· Preventing Parent-to-child transmission

· Focusing on IEC strategies for behaviour change in HRG, awareness among general population and demand-generation for HIV services

· Providing comprehensive care, support and treatment to eligible PLHIV

· Reducing stigma and discrimination through Greater involvement of PLHIV (GIPA)

· Ensuring effective use of strategic information at all levels of programme

· Integrating HIV services with the health system in a phased manner

· Mainstreaming HIV/AIDS activities with all key central- and state-level Ministries/departments and leveraging resources of the respective departments.

New WHO guidelines on treatment of HIV

New HIV treatment guidelines by WHO recommend offering antiretroviral therapy (ART) earlier. Recent evidence indicates that earlier ART will help people with HIV to live longer, healthier lives, and substantially reduce the risk of transmitting HIV to others. The move could avert an additional 3 million deaths and prevent 3.5 million more new HIV infections between now and 2025.

Call to initiate treatment at 500 CD4 cells/mm³ or less

The new recommendations encourage all countries to initiate treatment in adults living with HIV when their CD4 cell count falls to 500 cells/mm³ or less – when their immune systems are still strong. The previous WHO recommendation, set in 2010, was to offer treatment at 350 CD4 cells/mm³ or less. 90% of all countries have adopted the 2010 recommendation. A few, such as Algeria, Argentina and Brazil, are already offering treatment at 500 cells/mm3.

WHO has based its recommendation on evidence that treating people with HIV earlier, with safe, affordable, and easier-to-manage medicines can both keep them healthy and lower the amount of virus in the blood, which reduces the risk of passing it to someone else. If countries can integrate these changes within their national HIV policies, and back them up with the necessary resources, they will see significant health benefits at the public health and individual level, the report notes.

Further recommendations

The new recommendations also include providing antiretroviral therapy - irrespective of their CD4 count - to all children with HIV under 5 years of age, all pregnant and breastfeeding women with HIV, and to all HIV-positive partners where one partner in the relationship is uninfected. The Organization continues to recommend that all people with HIV with active tuberculosis or with hepatitis B disease receive antiretroviral therapy.

Another new recommendation is to offer all adults starting to take ART the same daily single fixed-dose combination pill. This combination is easier to take and safer than alternative combinations previously recommended and can be used in adults, pregnant women, adolescents and older children.

The Organization is further encouraging countries to enhance the ways they deliver HIV services, for example by linking them more closely with other health services, such as those for tuberculosis, maternal and child health, sexual and reproductive health, and treatment for drug dependence.

Challenges remain

Challenges still remain. Alongside the new treatment guidelines, a treatment progress update by WHO, UNAIDS, UNICEF identified areas in need of attention.

While the number of all eligible children on ART has increased by 10% between 2011 and 2012, this is still too slow compared to the 20% increase in adults. A further complication is that many key populations such as people who inject drugs, men who have sex with men, transgender people and sex workers, continue to face legal and cultural barriers that prevent them getting treatment that otherwise would be more easily available. Another factor that needs to be addressed is the significant proportion of people who, for many reasons, 'drop out' of treatment.

HIV vaccine: SAV001-H

Phase I Clinical Trial (SAV CT 01) of the first and only preventative HIV vaccine based on a genetically modified killed whole virus (SAV001-H) has been successfully completed with no adverse effects in all patients, Western and Sumagen Canada Inc. announced today.

Developed by Dr. Chil-Yong Kang and his team at the Schulich School of Medicine & Dentistry, with the support of Sumagen Canada, the vaccine (SAV001-H) holds tremendous promise for success in the final phases of clinical testing now that the first hurdle has been accomplished.

This vaccine is the first genetically modified killed whole virus vaccine (SAV001-H) in human clinical trial to evaluate its safety, tolerability and immune responses. The human clinical trial was initiated in March 2012 and completed in August 2013. This trial was a randomized, observer-blinded, placebo-controlled study of killed whole HIV-1 vaccine (SAV001-H) following intramuscular (IM) administration. HIV-infected, asymptomatic men and women, 18-50 years of age, have been enrolled in this study and randomized into two treatment groups to administer killed whole HIV-1 vaccine (SAV001-H) or placebo.

No serious adverse event was observed in any volunteer vaccines throughout the observation periods.

In addition to safety evaluation, HIV-1 specific antibody detections have been performed throughout the follow up period. The antibody against p24 capsid antigen increased as much as 64-fold in some vaccines and antibody against gp120 surface antigen increased up to eight-fold after vaccination. The increased antibody titers were maintained during the 52 week study period. The boost antibody production in HIV-positive volunteer vaccines is highly encouraging, since it forecasts a success of the Phase 2 human clinical trial, which will measure the immune responses.

In particular, the antibody against gp120 surface antigen is considered to be very important, since some of these antibodies may represent the broadly neutralizing antibodies, which seem to be the most important parameter of an effective HIV vaccine for prevention of HIV-infection.

HIV/AIDS has killed 35 million people worldwide, and more than 34 million people currently live with the virus infection. Since the virus was characterized in 1983, there have been numerous trials through pharmaceutical companies and academic institutions around the world to develop vaccines; however, no vaccine has been successful to date. Other HIV vaccines evaluated through human clinical trials have focused on either one specific component of HIV as an antigen, genetic vaccine using recombinant DNA, or recombinant viruses carrying the HIV genes. Kang's vaccine is unique in that it uses a killed whole HIV-1, much like the killed whole virus vaccines for polio, influenza, rabies and hepatitis A. The HIV-1 is genetically engineered so it is safer and can be produced in large quantities.

Health and recession

There is evidence that the full consequences of recessions may extend beyond employment to health broadly and behavioral health specifically. Seminal work by economist Christopher Ruhm raised the surprising possibility that health and health behaviors may actually *improve* during recessions (Ruhm, 1995, 2000). His central hypothesis was that recessions change the relative prices of both behaviors and goods and services that impact health, and economists

tend to believe that individuals respond to price changes in predictable ways. Ruhm suggested that during recessions people lose their job, permitting more time for investments in health (e.g., preparing healthy meals, exercise). This mechanism is often problematic for non-economists (and many economists), but when a person's opportunity cost of time (i.e., the income that could have been gained from working in this example) declines, the cost of time-intensive activities declines and economic theory predicts that the quantity demanded of these activities will increase. Moreover, reduced incomes attributable to recessions may prevent individuals from consuming health-harming goods such as alcohol, illicit drugs, and high calorie/high fat restaurant meals. Lastly, reduced work hours may protect against job-related strain, both physical and mental.

In a series of studies Ruhm found support for his hypotheses. For example, Ruhm shows that problematic alcohol use (e.g., alcohol-related traffic fatalities, binge drinking) declines in recessions (Ruhm, 1995, 2000; Ruhm and Black, 2002). Interestingly, the one health metric Ruhm found to decline during recessions was mental health (Ruhm, 2000). For this health outcome the recession-induced strain may off-set the protective mechanisms proposed by Ruhm.

Subsequent work on recessions and behavioral health has called to question some of Ruhm's findings, particularly for alcohol use (Davalos et al., 2012; Dee, 2001). Unlike Ruhm, these studies show that problematic alcohol use increases in recessions. Such studies suggest that during recessions individuals may self-medicate in response to increased economic stress. Further, these studies are more consistent with studies that focus on individual level employment (e.g., losing one's job) that show substance use levels are higher among those who experience unemployment. For example, Deb et al. (2011) find that adults who lose their job increase their daily alcohol consumption up to 42%. Ruhm's finding that mental health declines in recessions is generally supported by more recent research (Charles and DeCicca, 2008; Davalos and French, 2011; Tefft, 2011). Differences between studies may be driven by analysis of different recessions (Pacula, 2011). For example, the severe 2007 to 2009 recession is potentially more health harming that the relatively mild recessions of the early 1990s or 2000s.

Less controversial is the impact of recessions on health insurance. Because of the tight link between employment and health insurance in this country, access to health insurance (specifically employer-sponsored insurance) declines during recessions. Cawley et al. (2011) estimate that 9.3 million adult Americans lost health insurance due to a higher unemployment rate alone during the 2007 to 2009 recession. Lack of health insurance may prevent individuals from accessing needed health services. At the same time, federal, state, and local governments may reduce health services in recessions. For example, Willard et al. (2012) find that 53% of local health departments experienced cuts to their core funding during the most recent recession. Such cut backs may exacerbate access problems.

The recent recession has been shown to increase the new HIV infection rate amongst the Greeks by 50% in 2010 as compared to 2010. This has been in those who are intravenous drug abusers. This may have to do with the pared down needle exchange programme and increased drug abuse.

The research in Spain has shown that suicide rates in Spain have increased by 8% during this crisis. This is concentrated among the people who have recently lost job.

The recent crisis has also shown an increase in obesity. In Australia, the risk of being obese in 2010 was 20% higher among those who experienced financial stress in 2008 or 2009.

mTor and human health

Mammalian Target of Rapamycin or mTOR plays a particularly important role in metabolic organs — such as the liver, muscle, and fat tissue — to regulate whole body energy homeostasis. Thus, deregulation of mTOR signaling leads to metabolic disorders, such as obesity and type 2 diabetes, and cancer, that is, some of the most common causes of death in Western society. Furthermore, consistent with its role as a nutrient and growth factor sensor, decreased mTOR signaling reduces aging and thereby extends lifespan. Importantly, aging is a major risk factor for the development of cancer and metabolic disorders. Thus, mTOR underlies both aging and age-related diseases, suggesting that insight in mTOR signaling may provide a means to counter both aging and age-related disease by a single 'treatment'. In other words, an understanding of mTOR signaling may allow one to collectively 'treat' age-related diseases by delaying aging.

TOR in aging

Aging is defined as an accumulation of cellular damage over time, promoting disease and death. Genetic or pharmacological inhibition of TORC1 signaling extends lifespan in yeast, worms, flies and mice. Importantly, rapamycin delays the onset of age-related disease and extends lifespan even in old mice. When started at a young age, rapamycin also delays decline in cognitive function. Another intervention that slows the aging process is dietary restriction (DR) — a reduction in nutrient intake without malnutrition. DR prolongs lifespan in yeast, worms, flies, rodents, and possibly primates. In mammals, DR also retards the onset of age-related disease. At the molecular level, the life-extending effects of DR appear to be due largely to inhibition of TOR.

mTOR in cancer

mTOR is frequently activated in human cancers. Accumulating evidence suggests that aberrant regulation of both cell growth and metabolism significantly contribute to cancer development and progression. The notion of causal changes in metabolism during cancer development is supported by the observation that obesity and diabetes are risk factors for cancer and that diet can affect tumor growth.

Fasting, gut bacteria and longevity

Scientists have found that apart from virtues like healthy eating and exercising, calorie restriction can help achieve longevity and good health, the two major goals of biological research today.

A team of scientists in China have found that calorie restriction can enhance the population of gut microbes that have a positive co-relation with life span.

For their experiment, they divided mice in two groups: one was kept on a low fat diet and other on a high fat one. Each group was then subdivided into three smaller groups—one performed sedentary activity, second performed sedentary activity and was kept under 30 per cent calorie restriction and the last exercised but had no calorie restriction. When scientists analysed the type of microbes present in each of the six groups, some interesting facts came up. They noticed that with every change in diet and lifestyle the composition of microbial population in the gut of the mice also changed.

In their study, the scientists wrote that irrespective of whether the diet was high-fat or low fat, calorie restriction increased the population of bacterial species linked with longer life span and decreased those that were negatively correlated with lifespan. The group subjected to both low fat diet and calorie restriction turned out to be the healthiest at the end of the experiment. The gut population of this group had astonishingly high population of bacteria of Lactobacillus species and lowest levels of Streptococccae and TM7. Studies have shown that Lactobacilli increase gut's ability to fight infection whereas Streptococcae and TM7 perform no such roles and can be linked to inflammation. Yoghurt or curd, which is routinely consumed in Indian households, is loaded with Lactobacilli.

Many other aspects of calorie restriction have also been studied. A 2011 study, published in Biochemical and Biophysical Research Communications by a team of researchers from Central Drug Research Institute in Lucknow, evaluated the effect of calorie restriction on neurodegenerative disorders like Parkinson's disease. Working with Caenorhabditis elegans—the favourite worm of scientists for aging-related studies—they found that calorie restriction enhances production of sirtuin protein. "This protein mediates the protection of dopamine synthesizing neurons, thereby increasing the levels of neurotransmitter dopamine. We believe that calorie restriction can have major implications in prevention and cure of age-associated diseases like Parkinson's," says lead author Aamir Nazir.

He also says the same protein is produced in excess while exercising. This makes one wonder if calorie restriction can be a replacement for exercise. Aamir says the benefits of exercise span far beyond just burning calories. "Hence a healthy exercise regime cannot be replaced," he says. Aamir further cautions that the meaning of calorie restriction may vary from individual to individual and will depend on the body weight, fat storage and activity level.

Gut bacteria may help fight obesity

Different kinds of bacteria that live inside the gut can help spur obesity or protect against it, say scientists at Washington University in St. Louis who transplanted intestinal germs from fat or lean people into mice and watched the rodents change.

And what they ate determined whether the good germs could move in and do their job.

It raises the possibility of one day turning gut bacteria into personalized fat-fighting therapies, and it may help explain why some people have a harder time losing weight than others do.

We all develop with an essentially sterile digestive tract. Bacteria rapidly move in starting at birth — bugs that we pick up from mom and dad, the environment, first foods. Ultimately, the intestine teems with hundreds of species, populations that differ in people with varying health. Overweight people harbor different types and amounts of gut bacteria than lean people, for example. The gut bacteria we pick up as children can stick with us for decades, although their makeup changes when people lose weight, previous studies have shown.

To start finding out, Washington University graduate student Vanessa Ridaura took gut bacteria from eight people — four pairs of twins that each included one obese sibling and one lean sibling. One pair of twins was identical, ruling out an inherited explanation for their different weights. Using twins also guaranteed similar childhood environments and diets.

She transplanted the human microbes into the intestines of young mice that had been raised germ-free.

The mice who received gut bacteria from the obese people gained more weight — and experienced unhealthy metabolic changes — even though they didn't eat more than the mice who received germs from the lean twins, said study senior author Dr. Jeffrey Gordon, director of Washington University's Center of Genome Sciences and Systems Biology.

Then came what Gordon calls the battle of the microbes. Mice that harbored gut bacteria from a lean person were put in the same cages as mice that harbored the obesity-prone germs. The research team took advantage of an icky fact of rodent life: Mice eat feces, so presumably they could easily swap intestinal bugs.

What happened was a surprise. Certain bacteria from the lean mice invaded the intestines of the fatter mice, and their weight and metabolism improved. But the trade was one-way — the lean mice weren't affected.

Moreover, the fatter mice got the bacterial benefit only when they were fed a low-fat, high-fiber diet. When Ridaura substituted the higher-fat, lower-fiber diet typical of Americans, the protective bug swap didn't occur.

Why? Gordon already knew from human studies that obese people harbor less diverse gut bacteria. "It was almost as if there were potential job vacancies" in their intestines that the lean don't have, he explained.

Sure enough, a closer look at the mice that benefited from the bug swap suggests a specific type of bacteria, from a family named Bacteroidetes, moved into previously unoccupied niches in their colons — if the rodents ate right.

Determining the best combinations of intestinal bacteria to match a person's diet, and then growing those bugs in sterile lab dishes — like this study could — and turning them into pills.

Toxic nanoparticles entering humans through food

Ingestion of commonly encountered nanoparticles at typical environmental levels is unlikely to cause overt toxicity, according to US researchers. Nevertheless there is insufficient evidence to determine whether chronic exposures could lead to subtle alterations in intestinal immune function, protein profiles, or microbial balance.

Writing in a forthcoming issue of the *International Journal of Biomedical Nanoscience and Nanotechnology*, researchers have compared existing laboratory and experimental animal studies pertaining to the toxicity of nanoparticles most likely to be intentionally or accidentally ingested. Based on their review, the researchers determined ingestion of nanoparticles at likely exposure levels is unlikely to cause health problems, at least with respect to acute toxicity. Furthermore, in vitro laboratory testing, which often shows toxicity at a cellular level, does not correspond well with in vivo testing, which tends to show less adverse effects.

Ingrid Bergin in the Unit for Laboratory Animal Medicine, at the University of Michigan in Ann Arbor and Frank Witzmann in the Department of Cellular and Integrative Physiology, at Indiana University School of Medicine, in Indianapolis, explain that the use of particles that are in the nano size range (from 1 billionth to 100 billionths of a meter in diameter, 1-100 nm,

other thereabouts) are finding applications in consumer products and medicine. These include particles such as nano-silver, which is increasingly used in consumer products and dietary supplements for its purported antimicrobial properties. Nanoparticles can have some intriguing and useful properties because they do not necessarily behave in the same chemical and physical ways as non-nanoparticle versions of the same material.

Nanoparticles are now used as natural flavor enhancers in the form of liposomes and related materials, food pigments and in some so-called "health supplements." They are also used in antibacterial toothbrushes coated with silver nanoparticles, for instance in food and drink containers and in hygienic infant feeding equipment. They are also used to carry pharmaceuticals to specific disease sites in the body to reduce side effects. Nanoparticles actually encompass a very wide range of materials from pure metals and alloys, to metal oxide nanoparticles, and carbon-based and plastic nanoparticles. Because of their increasing utilization in consumer products, there has been concern over whether these small scale materials could have unique toxicity effects when compared to more traditional versions of the same materials.

Difficulties in assessing the health risks of nanoparticles include the fact that particles of differing materials and shapes can have different properties. Furthermore, the route of exposure (e.g. ingestion vs. inhalation) affects the likelihood of toxicity. The U.S. researchers evaluated the current literature specifically with respect to toxicity of ingested nanoparticles. They point out that, in addition to intentional ingestion as with dietary supplements, unintentional ingestion can occur due to nanoparticle presence in water or as a breakdown product from coated consumer goods. Inhaled nanoparticles also represent an ingestion hazard since they are coughed up, swallowed, and eliminated through the intestinal tract.

Based on their review, the team concludes that, "Ingested nanoparticles appear unlikely to have acute or severe toxic effects at typical levels of exposure." Nevertheless, they add that the current literature is inadequate to assess whether nanoparticles can accumulate in tissues and have long-term effects or whether they might cause subtle alterations in gut microbial populations. The researchers stress that better methods are needed for correlating particle concentrations used for cell-based assessment of toxicity with the actual likely exposure levels to body cells. Such methods may lead to better predictive value for laboratory in vitro testing, which currently over-predicts toxicity of ingested nanoparticles as compared to in vivo testing.

Genetically modified rice as cure for rotavirus diarrhoea

Rotaviruses are one of the leading causes of severe diarrhoea in children across the world. According to WHO estimates, 527,000 children under five, most of them from low-income countries, die of rotavirus infections annually. At present, live vaccines are available to combat the virus. However, there have been some reports of infections induced from vaccines.

Researchers have tweaked the genes of a rice variety to make it produce antibodies against rotavirus. The antibody is found naturally in llamas, which are resistant to rotavirus. Researchers engineered the rice , dubbed as MucoRice ARP1, by introducing rotavirus antibody gene from llamas in rice genome. They tested their newly-developed rice variety on both normal and immune deficient mice. "It markedly decreased the viral load in immunocompetent and immunodeficient mice," the report says.

The antibody was found to work fine even after year-long storage and heat treatment at 94°C for 30 minutes.

The researchers say the present study markedly extends the potential of rice plants into an antibody production system and can form the basis for orally administered medicine against rotavirus infections. "MucoRice-ARP1 rice powder or rice water offer what we believe are novel approaches to the prevention and treatment of rotavirusinduced diarrhoea. It may be used to reduce the medical and economic burden in both developed and developing countries," the study notes.

The researchers observe that vaccines have poor effect on immunocompromised individuals and usage of live vaccines could sometimes backfire.

Hence they regard passive immunotherapy (antibodies) as the only available intervention that can offer protection. Though oral administration of antibodies works well as both prevention and therapy in individuals with rotavirus induced diarrhoea, the production and purification of antibodies is a costly proposition, say the researchers.

P Suresh Kumar, senior scientist at the National Institute of Abiotic Stress Management in Pune says, "Rice being the major staple crop among Indians, the result is highly relevant and encouraging for scientists and policy makers to develop rice strains that bear rotavirus antibody to act against diarrhoea."

"The important aspect of plant based antibody system is that large amounts of antibodies can be produced at a low cost. In contrast with previous systems, there is no need for purification for this transgenic rice," says Kumar. "As MucoRice-ARP1 originates from edible rice seeds, the obtained rice powder can be directly used as an ingredient in a broad range of nutraceuticals."

Kumar informs that unlike antibody producing tobacco leaves and tomatoes, which require storage under low temperature, antibody-producing cereals such as rice and wheat as well as pea seeds can be stored at room temperature.

It remains to be seen if the genetically modified rice is safe or not.

Infant formula feed potentially harmful

It is common knowledge that breast milk is the best diet for newborns. Several studies have even linked infant formula with chronic diseases such as obesity and type II diabetes in adulthood. The basis of this link has, however, been unclear. Researchers have found that feeding formula causes metabolic stress in infants and this causes complications later in life.

The researchers used rhesus monkey infants as human stand-ins for the study. Two groups of five monkeys each were given two different dietary treatments. One group was fed standard infant formula and other breast milk since birth. All the monkeys had same weight at birth but after three months it was found that formula-fed infants had grown faster than the ones fed with breast milk. The study explains that a higher rate of growth at this stage leads to adult obesity.

Formula feeding may lead to other complications as well. The study notes that higher growth rate in infants has also been linked with insulin resistance in adults. The results confirmed higher insulin levels in serum of formula-fed individuals, which could set stage for insulin resistance. Formula-fed infants also showed pro-inflammatory responses that are immune

system's reaction to injury or pathogens. This supports the hypothesis that formula feeding affects the immune system of infants, too.

Lactose level in excreta of formula-fed infants was also found to be higher than that of breast-fed ones. This, the study explains, could be indicative of damage to the intestinal lining.

BPA and BSP and human health

A study has shown that a mixture of BPA, Bisphenol S (BPS) and nylophenol (NP) can incur much greater damage than what these known hormone-disruptors can cause in isolation. What is worse, such chemical mixtures are fairly common in our environment.

Estrogens are key hormones in humans. Though produced in minute quantities, they regulate important reproductive functions in both males and females. Alarmingly, today's man-altered world consists of several compounds that can mimic these hormones, interfering significantly with the bodily functions in the long run. BPA is the most common of such estrogen-mimics. In commercial use since 1957, the hormone-disruptor is commonly found in plastic goods, inner lining of metal food cans and drums and thermal-paper used in receipts.

As more and more people became aware, and wary, of the ill-effects of BPA in the past few years, BPS was introduced as a safer alternative. But studies have shown that pre-release tests with BPS missed some key facts—recent in vitro tests have revealed that BPS also acts as an estrogen-mimic even at very low concentrations. So next time you see BPA-free written on your water bottle, be aware that it has got BPS instead, and that is not a safe option either. NP, a surfactant commonly used in industrial applications and for cleaning oil spills, is another estrogen-mimic.

Cheryl S Watson and Rene Vinas of department of biochemistry and molecular biology at the University of Texas Medical Branch in Galveston, US, have been studying BPA, BPS and NP for a long time. One fact that bothered them was that these estrogen-mimics are never present in the atmosphere in isolation but always as mixtures. How were these mixtures affecting the human body?

"Working with lab-grown rat pituitary cells, we found that mixtures of these environmental estrogens, even at very low concentrations, disrupted hormonal signalling of natural estrogens. This disruption was greater than what single environmental estrogens do," states their paper.

"Environmental estrogens activate or inactivate enzymes in patterns different from normal hormones. They also alter normal cell birth and death and disrupt the secretion of another hormone, prolactin," says Watson. Such disruptions can wreak havoc on vital body functions like reproduction, development, offspring survival and behaviour, among others.

The scientists chose rat pituitary cells for their study because "they are from the "master gland" that controls hormone secretion and responses of many other glands and organs. Therefore, if a disruption occurs in these kinds of cells, it can affect the whole body."

"Plastics are useful and we cannot take drastic measure of eliminating them completely, but we have to be rational in avoiding toxins in plastics and ensure they do not leach out toxic stuff," says Kannan Kurunthachalam, research scientist at Wadsworth Center of the New York State Department of Health. He has done pioneering work on measuring BPA and BPS levels in the urine of western and Asian populations, including Indians. "We can also try to

find a way to use plastics wherein human and environmental exposures can be minimised or eliminated," adds Kurunthachalam.

Copper alloys to reduce bacterial load in hospitals

Copper utensils have been used in Indian households since ages due to the anti-microbial properties of the metal. It has now been found that copper alloys can also help reduce infections in hospitals drastically.

It is estimated that nearly 100,000 billion people die of healthcare-associated infections in the US, while 10-30 per cent patients develop infections in Indian hospitals and nursing homes. Researchers from Medical University of South Carolina, Memorial Sloan-Kettering Cancer Center and Ralph H Johnson Veterans Affairs Medical Center in the US suggest copper could be used to control these infections.

To test the efficacy of the metal, they used copper alloys, registered with the US Environmental Protection Agency, on six frequently touched objects—bed rails, bed tables, intravenous poles, chair arms, call button and monitors—in the Intensive Care Units (ICU) of three hospitals. At the end of the study, it was found that copper fixtures reduced the infections in the three ICUs by more than half. Findings of the study were published in Infection Control and Hospital Epidemiology in May 2013.

"There is enough scientific evidence from clinical trials that evaluate the efficacy of copper alloys in reducing bacterial load," says study co-author, Michael Schmidt of the department of microbiology and immunology at Medical University of South Carolina. M C Yadavannavar, professor of community medicine at Shri B M Patil Medical College, Bijapur, says a few Indian hospitals, like AIIMS in New Delhi and PGI in Chandigarh, are embracing antimicrobial copper in ICU design.

Eritoran, a novel approach to treating Swine flu

MOST bird and swine flu deaths in humans occur due to an inability to breathe. It happens because the body, in its effort to kill the influenza virus, elicits a frenzied immune response which causes severe inflammation in the lungs. This leads to lung damage and hindered breathing and in most cases death. Treating the disease gets difficult day by day as flu viruses evolve rapidly. New viral strains are unaffected by any immunity that a population may have developed against older ones.

Researchers led by Kari Ann Shirey and Stefanie N Vogel of the University of Maryland in the US have now taken a new approach to treat the disease. Instead of the ever-evolving virus they are targeting human body's immune response to the virus to prevent flu-related deaths. And they have found a drug which does just that. Still under pre-clinical trial, eritoran has been found to greatly reduce lung inflammation and deaths in mouse models infected with swine flu viruses currently circulating among humans—H1N1 and H3N2. The treatment also suppressed the genes that cause inflammation.

"Our data suggests that eritoran blocks the cytokine storm induced by influenza by reducing the generation of oxidized phospholipids derived from host cells," says Vogel. The study, published in Nature on May 1, shows eritoran works against flu and other respiratory infections in isolation as well as in combination with existing treatments.

"This pre-clinical study proves that eritoran is effective against influenza in mice. It is different from current anti-influenza therapies and might be very useful because it is still effective when given after six days of infection," says Hongzhou Lu, a professor at the Shanghai Public Health Clinical Center at Fudan University in Shanghai, China. "Although this study showed a positive result, it still needs validation in humans," says Hongzhou.

According to D T Mourya, the director of National Institute of Virology in Pune, different influenza strains can behave differently due to a difference in their ability to cause disease. Thus, the drug needs to be tested against the latest Influenza virus H7N9 also. "People in India are at as much risk as elsewhere due to the newer emerging influenza strains, says Mourya.

Battle against drug resistant malaria

One of the most challenging features of malarial parasite Plasmodium falciparum is its ability to evolve and render anti-malarial drugs ineffective. The emergence of multidrug resistant strains of the parasite in South-East Asia and other tropical countries in recent years is undermining international efforts to eradicate malaria. So much so that in April the WHO announced investing $400 million to combat resistant strains of the debilitating disease.

A recent study by researchers from the Central Drug Research Institute of Council of Scientific and Industrial Research (CSIR-CDRI), in Lucknow, holds out fresh hope for conquering the disease. CSIR-CDRI scientists have found that an antifungal drug can kill multidrug-resistant malaria parasite in mice by enhancing the efficacy of widely used, artimisinin-based anti-malarial drugs artesunate, artemether and arteether.

The scientists had earlier demonstrated that the antifungal drug, ketoconazole, could reverse the resistance of P falciparum to anti-malarial drug mefloquine. Ketoconazole, works by inhibiting the activity of cytochrome P450 3A4 (CYP3A4), an enzyme found in liver. Inhibition of the activity of CYP3A4 slows down the metabolism of mefloquine and thus prolongs its plasma life or the time period for which the drug remains in blood, says one of the authors Renu Tripathi. A prolonged plasma life enhances the anti-malarial activity of mefloquine to the extent that it can act against the resistant P falciparum.

To find out the efficacy of ketoconazole on artimisinin-based anti-malarial drugs, the researchers tested it on mice infected with multi-drug resistant Plasmodium yoelli nigeriensis, which is known to cause malaria in rodents. When ketoconazole was used in combination with artimisinin-based drugs, it cured the infected mice. Analysis of their livers revealed that CYP3A4 enzyme was suppressed by 59 per cent in mice treated with both ketoconazole and artimisinin-based drugs, while the enzyme was not suppressed in mice treated with the drugs alone.

"Inhibition of CYP3A4 enzyme slowed down the conversion of artimisinin into its metabolite, dihydroartemisinin. This increases its anti-malarial activity," says Tripathi. The therapeutic approach can lower the effective dose of artimisinin-based drugs, reducing the cost of malaria treatment, she adds.

Malarial Vaccine

A malaria vaccine has become the first to provide 100% protection against the disease, confounding critics and far surpassing any other experimental malaria vaccine tested. It will now be tested further in clinical trials in Africa.

The results are important because they demonstrate for the first time the concept that a malaria vaccine can provide a high level of protection, says Anthony Fauci, director of the US National Institute of Allergy and Infectious Diseases in Bethesda, Maryland, adding that the findings are cause for "cautious optimism".

No effective malaria vaccine is available at present. The World Health Organization has set a target to develop a malaria vaccine with 80% efficacy by 2025, but until now, says Fauci, "we have not even gotten anywhere near that level of efficacy."

Scientists had previously been sceptical of the vaccine because producing it required overcoming massive logistical hurdles. The vaccine — called PfSPZ because it is made from sporozoites (SPZ), a stage in the life cycle of the malarial parasite *Plasmodium falciparum* (Pf) — uses a weakened form of the whole parasite to invoke an immune response.

In the phase I safety trial, reported today in *Science*, the six subjects given five doses intravenously were 100% protected from later challenge by bites of infectious mosquitoes, whereas five of six unvaccinated controls developed malaria — as did three of nine people given only four doses of the vaccine.

PfSPZ was developed by Sanaria, a company based in Rockville, Maryland, and led by Stephen Hoffman, a veteran malaria researcher who also led the PfSPZ clinical trial. Most malaria-vaccine candidates are recombinant-subunit vaccines containing just a handful of parasite proteins, but Hoffman decided to test the whole-sporozoite vaccine on the basis of past experiments dating back to the 1970s showing that strong and long-lived protection could be obtained by exposing volunteers to thousands of bites from irradiated infected mosquitoes.

That the vaccine works so well is a "pivotal success," says Stefan Kappe, a malaria researcher at the Seattle Biomedical Research Institute in Washington."The trial results constitute the most important advance in malaria vaccine development since the first demonstration of protection with radiation attenuated sporozoite immunization by mosquito bite in the 70s."

Against the odds

But to make PfSPZ was challenging. Sanaria succeeded in raising mosquitoes in sterile conditions on an industrial scale, feeding them blood infected with the malaria parasite and then irradiating them to weaken the parasite so that it can still infect people but not cause disease.

Billions of parasites were then harvested from the mosquitoes' salivary glands, purified and cryopreserved. Many researchers were highly sceptical that sporozoites could be mass-produced in a way that passed the strict quality and safety standards needed for human medicines, notes Fauci. "To my amazement, Hoffman did it," he adds.

Hoffman says that he hopes to have a vaccine licensed within four years. The trial now needs to be repeated and extended in regions where malaria is rampant to test whether it provides protection against different strains of the parasite than that used in the vaccine, and to see

how it performs in different age groups, including young children. The first trials will be carried out at the Ifakara Health Institute in Tanzania.

Piggybacking infrastructure

Even if the vaccine is shown to be highly effective in the field, logistical difficulties might limit its applicability. In mass vaccination campaigns, hundreds of people are vaccinated within minutes, so vaccines are usually given orally or by injection into or just under the skin. Intravenous injection is more cumbersome. "It's very unlikely to be deployable in infants or young children," argues Adrian Hill, a malaria researcher at the Jenner Institute in Oxford, UK.

In 2011, a clinical trial of PfSPZ given under the skin reported disappointing results, protecting only two of 80 subjects. But the need to deliver the vaccine intravenously "is not a show-stopper", says Hoffman, noting that the volume of vaccine — 0.5 millilitres — is tiny and requires a tiny syringe, although the company is exploring ways to improve the intravenous delivery system.

Another logistical hurdle, says Hill, is that the vaccine must be kept frozen in liquid nitrogen vapour phase. Hoffman argues, however, that the vaccine can piggyback on veterinary infrastructure in places that use liquid nitrogen to store and transport veterinary vaccines and semen for artificial insemination of livestock. "If you can carry semen into the deep Saharan belt and remote areas, why can't you do that for a human vaccine?" says Marcel Tanner, director of the Swiss Tropical and Public Health Institute in Basel, Switzerland, which is a sponsor of the trial in Tanzania.

"Which of the logistical challenges can be managed and which will become show-stoppers can be difficult to predict," says David Kaslow, director of the PATH Malaria Vaccine Initiative in Washington, DC, a public–private partnership for malaria-vaccine development.

Hygiene hypothesis

According to the 'hygiene hypothesis', the decreasing incidence of infections in western countries and more recently in developing countries is at the origin of the increasing incidence of both autoimmune and allergic diseases.

The hygiene hypothesis is based upon epidemiological data, particularly migration studies, showing that subjects migrating from a low-incidence to a high-incidence country acquire the immune disorders with a high incidence at the first generation. However, these data and others showing a correlation between high disease incidence and high socio-economic level do not prove a causal link between infections and immune disorders. Proof of principle of the hygiene hypothesis is brought by animal models and to a lesser degree by intervention trials in humans. Underlying mechanisms are multiple and complex. They include decreased consumption of homeostatic factors and immunoregulation. These mechanisms could originate, to some extent, from changes in microbiota caused by changes in lifestyle, particularly in inflammatory bowel diseases. Taken together, these data open new therapeutic perspectives in the prevention of autoimmune and allergic diseases.

Infants whose parents suck on the pacifier to clean it transfer microbes from their saliva to their children.

Such kids have been found to be 37 per cent less likely to develop eczema or allergies and 12 per cent less likely to have asthma than children whose parents cleaned the pacifier by rinsing it in water.

Kids and teens who move to the US are 44 per cent less likely to have an allergic condition, like asthma, eczema or pollen and food allergies, as compared to those who are born there, shows a study based on data from the National Survey of Children's Health. However, the risk of allergies increases as foreign-born children spend more time in the US. Foreign-born children who live in the US for over 10 years are more likely to have allergies than those who lived there for two years or less.

The finding is in line with "hygiene hypothesis" that says bodies of kids brought up in overly sterilized environments never learn how to fight pathogens.

False memory implanted in mice brains

Scientists have implanted a false memory in the brains of mice in an experiment that they hope will shed light on the well-documented phenomenon whereby people "remember" events or experiences that have never happened.

False memories are a major problem with witness statements in courts of law. Defendants have often been convicted of offences based on eyewitness testimony, only to have their convictions later overturned when DNA or some other corroborating evidence is brought to bear.

In order to study how these false memories might form in the human brain, Susumu Tonegawa, a neuroscientist at the RIKEN-MIT Center for Neural Circuit Genetics, and his team encoded memories in the brains of mice by manipulating individual neurons.

Memories of experiences we have had are made from several elements including records of objects, space and time. These records, called engrams, are encoded in physical and chemical changes in brain cells and the connections between them. According to Tonegawa, both false and genuine memories seem to rely on the same brain mechanisms.

In their work, Tonegawa's team used a technique known as optogenetics, which allows the fine control of individual brain cells. They engineered brain cells in the mouse hippocampus, a part of the brain known to be involved in forming memories, to express the gene for a protein called channelrhodopsin. When cells that contain channelrhodopsin are exposed to blue light, they become activated. The researchers also modified the hippocampus cells so that the channelrhodopsin protein would be produced in whichever brain cells the mouse was using to encode its memory engrams.

In the experiment, Tonegawa's team placed the mice in a chamber and allowed them to explore it. As they did so, relevant memory-encoding brain cells were producing the channelrhodopsin protein. The next day, the same mice were placed in a second chamber and given a small electric shock, to encode a fear response. At the same time, the researchers shone light into the mouse brains to activate their memories of the first chamber. That way, the mice learned to associate fear of the electric shock with the memory of the first chamber.

In the final part of the experiment, the team placed the mice back in the first chamber. The mice froze, demonstrating a typical fear response, even though they had never been shocked

while there. "We call this 'incepting' or implanting false memories in a mouse brain," Tonegawa told Science.

A similar process may occur when powerful false memories are created in humans.

"Humans are very imaginative animals," said Tonegawa. "Independent of what is happening around you in the outside world, humans constantly have internal activity in the brain. So, just like our mouse, it is quite possible we can associate what we happen to have in our mind with bad or good high-variance ongoing events. In other words, there could be a false association of what you have in your mind rather than what is happening to you."

He added: "Our study showed that the false memory and the genuine memory are based on very similar, almost identical, brain mechanisms. It is difficult for the false memory bearer to distinguish between them. We hope our future findings along this line will further alert legislatures and legal experts how unreliable memory can be."

He cautioned that the false memories created in the mice in the experiments were far simpler than the complex false memories that have generated controversy within psychology and psychiatry, for example false memories of childhood sexual abuse, or even memories for bizarre ritualised satanic abuse, abduction by aliens, or "past lives".

"Such rich false memories will clearly involve many brain systems and we are still a long way from understanding the processes involved in their formation at the neuronal level," said Prof French.

"It is unlikely that this kind of pairing could lead to the rich set of associations related to normal memories, although it is possible that over time such pairing could be integrated with other memories to construct a more elaborate false narrative."

The mouse models created by the MIT team will help scientists ask ever more complex questions about memories in people. "Now that we can reactivate and change the contents of memories in the brain, we can begin asking questions that were once the realm of philosophy," said Steve Ramirez, a colleague of Tonegawa's at MIT.

"Are there multiple conditions that lead to the formation of false memories? Can false memories for both pleasurable and aversive events be artificially created? What about false memories for more than just contexts – false memories for objects, food or other mice? These are the once seemingly sci-fi questions that can now be experimentally tackled in the lab."

As the technology develops, said French, scientists need to think about its uses carefully. "Whatever means are used to implant false memories, we need to be very aware of the ethical issues raised by such procedures - the potential for abuse of such techniques cannot be overstated."

Dermcidin in sweat might help fight superbugs

It is a losing battle for conventional antibiotic drugs. Many of them can no longer effectively control or kill their target microbes. The threat of antibiotic resistance in pathogenic bacteria has necessitated development of new antimicrobials, called the next-generation antibiotics. Scientists have now found that dermcidin, a compound produced naturally by the body, can act as a potent antimicrobial agent.

The human body, particularly the skin and the mouth, is constantly exposed to a variety of bacteria but still maintains a healthy stable state. Skin, the first host tissue to encounter atmospheric bacteria, responds through an elaborate signalling network. It produces antimicrobial peptides (AMPs) and small protein molecules (cytokines) which trigger immune responses. These naturally occurring classes of antimicrobials have novel mechanisms of action, which ensure that microbes have little chance to develop resistance and are effective against a broad spectrum of bugs, including bacteria, fungi and virus. They are, therefore, promising alternatives or augmenters of synthetic antibiotic therapies.

Dermcidin, one of the most important AMPs secreted by sweat glands of the skin, is known to be robustly active against a wide range of disease-causing bacteria such as drug-resistant Staphylococcus aureus and Mycobacterium tuberculosis. A research team led by Chen Song, of Computational Biomolecular Dynamics Group at Max Planck Institute for Biophysical Chemistry in Germany, examined the antimicrobial mechanism of dermcidin. The researchers found that it efficiently damages bacterial cell membrane by producing ion channels across the cellular envelop in the presence of zinc ions. Cell membrane integrity is essential for bacterial cell survival and development of antibiotic resistance. Their X-ray, electrophysiology and simulation data suggests that such channels are highly permeable to water and ions and allow their uncontrolled flow across the membrane, eventually killing harmful microbes. The study also shows that dermcidin can adapt to different types of bacterial membranes. This explains why it is an efficient, broadspectrum antibiotic, which can ward off both bacteria and fungi.

Technological paradigms for food security

Food security involves availability, accessibility and affordability of food. It also includes the ability of the body to absorb the food. All these aspects are profoundly affected by technological progress.

With relation to availability, the most important aspect is increase in the farm productivity. It has been brought about by a combination of myriad technological advances. Probably the single most important factor has been the introduction of hybrid varieties that led to the green revolution across the world. Another important factor has been farm mechanisation. It includes the use of tractors, threshers, etc. It has enabled more productive use of the labour in agriculture.

The introduction of electric pumps and canals that enabled large areas to be brought under irrigation has also contributed immensely. Use of sprinklers and drip irrigation has economised the use of water in agriculture. The use of fertilizers, pesticides and other synthetic chemicals cannot be ignored either. Further, the latest innovation in the form of genetically modified crops promises to usher a new era in agricultural productivity. Soil testing technologies are also important contributors in the march towards sustainable development. The use of biopesticides and biofertilizers are also steps in the same direction. Precision farming and the use of GPS in agriculture also promises to increase productivity. Nanotechnology is also a promising field that is helping increase productivity in farm sector.

Apart from these direct interventions, other important innovations include the use of ICT to help farmers improve the productivity as well as the returns from their produce. The farmers in India also get timely weather updates on through SMS on their mobiles which has also helped increase the productivity.

Further, the productivity from allied activities has also increased thanks to similar factors like hybridisation, mechanisation, etc. These include the fisheries and the dairy sectors.

The accessibility aspect has been answered with the introduction of modern technologies for the safe transfer of food from the farm to the fork. These include good roads, good warehousing facilities and the ubiquitous PDS. The use of technology in the PDS in Tamil Nadu has given fantastic returns in the form of reduction in pilferage and diversion of the PDS foodgrains.

The affordability has been improved thanks to the passing of the NFS Act and promised use of Adhaar to maximise the benefits to the deserving and minimising diversion and corruption. The use of technology has also lead to an improved productivity which has lead to increased purchasing power and hence affordability. Technology being harnessed to improve financial inclusion also improves the affordability and hence food security.

The absorption has improved following use of technology in the form of vaccinations, safe drinking water, tele-medicine, etc. The use of better technology in the health sphere and its reach to the poorest through the NRHM and other health schemes has ensured improved absorption of food by the body.

Hence, technology and food security are intrinsically linked and the future definitely belongs to greater use of technology in ensuring that the world is able to feed its growing population.