# New epilepsy treatment offers 'on demand' seizure suppression

A new treatment for drug-resistant epilepsy with the potential to suppress seizures 'on demand' with a pill, similar to how you might take painkillers when you feel a headache coming on, has been developed by UCL (University College London) researchers funded by the Wellcome Trust.

The treatment, described in Nature Communications, combines genetic and chemical approaches to suppress seizures without disrupting normal brain function. The technique was demonstrated in rodents but in future we could see people controlling seizures on-demand with a simple pill.

Epilepsy affects around 50 million people worldwide including 600,000 in the UK and around a quarter of cases are resistant to conventional treatments. Many of these cases could be addressed by the new treatment method, which relies on genetic modification of brain cells to make them sensitive to a normally inactive compound.

"First, we inject a modified virus into the area of the brain where seizures arise," explains Professor Dimitri Kullmann of the UCL Institute of Neurology, senior author of the research. "This virus instructs the brain cells to make a protein that is activated by CNO (clozapine-N-oxide), a compound that can be taken as a pill. The activated protein then suppresses the over-excitable brain cells that trigger seizures, but only in the presence of CNO.

"At the moment, severe seizures are treated with drugs that suppress the excitability of all brain cells, and patients therefore experience side effects. Sometimes the dose required to stop seizures is so high that patients need to be sedated and taken to intensive care. If we can take our new method into the clinic, which we hope to do within the next decade, we could treat patients who are susceptible to severe seizures with a one-off injection of the modified virus, and then use CNO only when needed.

"CNO would be given as a pill in the event that patients could predict when seizures were likely to occur. For example, many people with treatment-resistant epilepsy experience clusters of seizures, where severe seizures are preceded by smaller ones. Seizure risk is also high when people are ill, sleep deprived, or at certain times of the menstrual cycle, so these would all be good times to take the pill as a preventative measure. In urgent situations, the compound could be given as an injection. We could even consider a fully automatic delivery system, where CNO was given by a pump, as is done for insulin in some people with diabetes."

As CNO has a half-life of about a few hours and only affects the pre-treated epileptic parts of the brain, the new method avoids the need to permanently alter the brain or treat the whole brain with seizure-suppressing drugs. It builds on similar work by Professor Kullmann's group using gene therapy to 'calm down' brain cells, or using light pulses to activate seizure-suppressing receptors in the brain. The new technique works in a similar way but is reversible and avoids the need for invasive devices to deliver light to the brain.

"After the one-off injection into affected areas of the brain, our new technique would require nothing beyond CNO, administered as an injection or a pill, to suppress seizures when required," says Professor Kullmann. "This makes it more attractive than alternative forms of targeted therapy such as surgery to remove the brain region where seizures arise, or gene therapy that permanently alters the excitability of brain cells.

"Although there is currently no evidence that permanently suppressing excitability in a small area affects brain function, we cannot be sure that it would have no impact long-term. Our new method is completely reversible, so if there were any side-effects then people could simply stop taking the CNO pill."

Dr John Williams, head of clinical activities, neuroscience and mental health at the Wellcome Trust said: "Epilepsy is a debilitating condition with limited treatment options available to the 50 million people affected globally. We look forward to seeing how this innovative approach for targeted control of seizure activity might translate into new treatments options for managing and controlling seizures in humans."

# Smokers with gene defect have one in four chance of developing lung cancer

Around a quarter of smokers who carry a defect in the BRCA2 gene will develop lung cancer at some point in their lifetime, a large-scale, international study reveals.

Scientists announce a previously unknown link between lung cancer and a particular BRCA2 defect, occurring in around 2 per cent of the population, in research published in Nature Genetics today (Sunday).

The defect in BRCA2 -- best known for its role in breast cancer -- increases the risk of developing lung cancer by about 1.8 times.

Smokers as a group have a high lifetime risk of around 13 per cent (16 per cent in men and 9.5 per cent in women). The new study therefore suggests around one in four smokers with the BRCA2 defect will develop lung cancer.

Around 10 million adults in Great Britain smoke, which means that up to around 200,000 adult smokers could have the specific BRCA2 defect, known as BRCA2 c.9976T.

The researchers, led by a team at The Institute of Cancer Research, London, compared the DNA of 11,348 Europeans with lung cancer and 15,861 without the disease, looking for differences at specific points in their DNA. The team was mainly funded by the US National Institute of Health, with additional support from Cancer Research UK

The link between lung cancer and defective BRCA2 -- known to increase the risk of breast, ovarian and other cancers -- was particularly strong in patients with the most common lung cancer sub-type, called squamous cell lung cancer. The researchers also found an association between squamous cell lung cancer and a defect in a second gene, CHEK2, which normally prevents cells from dividing when they have suffered damage to their DNA.

The results suggest that in the future, patients with squamous cell lung cancer could benefit from drugs specifically designed to be effective in cancers with BRCA mutations. A family of drugs called PARP inhibitors have shown success in clinical trials in breast and ovarian cancer patients with BRCA mutations, although it is not known whether they could be effective in lung cancer.

Study leader Professor Richard Houlston, Professor of Molecular and Population Genetics at The Institute of Cancer Research (ICR), said: "Our study showed that mutations to two genes, BRCA2 and CHEK2, have a very large effect on lung cancer risk in the context of smoking. Mutated BRCA2 in particular seems to increase risk by around 1.8 times.

"Smokers in general have nearly a 15 per cent chance of developing lung cancer, far higher than in non-smokers. Our results show that some smokers with BRCA2 mutations are at an enormous risk of lung cancer -- somewhere in the region of 25 per cent over their lifetime.

"Lung cancer claims more than a million lives a year worldwide and is by far the biggest cancer killer in the UK. We know that the single biggest thing we can do to reduce death rates is to persuade people not to smoke, and our new findings make plain that this is even more critical in people with an underlying genetic risk."

Professor Paul Workman, Deputy Chief Executive of The Institute of Cancer Research, said: "These findings indicate that around a quarter of smokers with a specific defect in their BRCA2 gene will develop lung cancer -- a disease which is almost invariably fatal. All smokers are taking a considerable risk with their health, regardless of their genetic profile, but the odds are stacked even more heavily against those with this genetic defect who smoke."

# More than two-thirds of healthy Americans are infected with human papilloma viruses

In what is believed to be the largest and most detailed genetic analysis of its kind, researchers at NYU Langone Medical Center and elsewhere have concluded that 69 percent of healthy American adults are infected with one or more of 109 strains of human papillomavirus (HPV). Only four of the 103 men and women whose tissue DNA was publicly available through a government database had either of the two HPV types known to cause most cases of cervical cancer, some throat cancers, and genital warts.

Researchers say that while most of the viral strains so far appear to be harmless and can remain dormant for years, their overwhelming presence suggests a delicate balancing act for HPV infection in the body, in which many viral strains keep each other in check, preventing other strains from spreading out of control. Although infection is increasingly known to happen through skin-to-skin contact, HPV remains the most common sexually transmitted infection in the United States. It is so common that experts estimate nearly all men and women contract some strain of it during their lives.

"Our study offers initial and broad evidence of a seemingly 'normal' HPV viral biome in people that does not necessarily cause disease and that could very well mimic the highly varied bacterial environment in the body, or microbiome, which is key to maintaining good health," says senior study investigator and NYU Langone pathologist Zhiheng Pei, MD, PhD. Dr. Pei, an associate professor at NYU Langone, plans to present his team's findings on May 20 in Boston at the annual meeting of the American Society for Microbiology.

Lead study investigator and NYU Langone research scientist Yingfei Ma, PhD, says "the HPV 'community' in healthy people is surprisingly more vast and complex than previously thought, and much further monitoring and research is needed to determine how the various non-cancer-causing HPV genotypes interact with the cancer-causing strains, such as genotypes 16 and 18, and what causes these strains to trigger cancer."

For the study, which took two years to complete, researchers analyzed data made publicly available from the National Institutes of Health (NIH) Human Microbiome Project, which is gathering information on microorganisms' effects on human health. The NIH data consisted of comprehensive DNA analyses assembled by a technique called shotgun sequencing. The DNA decoding technique helped sort through vast amounts of genetic material among 748 tissue swabs of study participants' major organs, including skin, vagina, mouth, and gut. Tissue samples were originally collected from healthy study volunteers, ages 18 to 80, participating in the NIH project. In shotgun sequencing, the genetic code of long strands of DNA is deciphered in a random firing pattern, much like pixels in a photo, until a full picture becomes apparent.

Dr. Pei cautions that until the harm or benefits of the many HPV strains become apparent, people should not be overly concerned, but consult their physician or an infectious disease specialist to assess any potential threat before seeking any antiviral or other therapy. In addition, he says getting vaccinated against types 16 and 18 is still "a good idea," especially for preventing cervical cancer, until broader, more comprehensive anti-HPV vaccines become available that also target cancers in other body organs and tissues.

Among the study's other key findings:

- Some 109 of 148 known HPV types were detected in study participants.

- Most study participants had HPV infections in the skin (61 %); then vagina (41 %), mouth (30 %), and gut (17 %).

- Of the 71 study participants infected with HPV, 42 (59 %) had HPV in only one organ, 22 (31 %) had it in two organs, and seven (10 %) had it in three; none had HPV in all four organs tested.

- Skin samples contained the most varied HPV strains (80 types of HPV, including 40 that were found only in the skin). Vaginal tissue had the second most numerous strains (43 types of HPV, with 20 strains exclusive to the organ), followed by mouth tissue (33 types, of which five were exclusively oral in origin), and gut tissue (six types, all of which were found in other organs).

Dr. Pei says his team's study results also highlight the weaknesses in current clinical test kits for HPV, currently designed to recognize only a dozen or more viral types most closely tied to cervical cancer. He says broader detection methods and comprehensive diagnostic tests are needed to more accurately assess people's "true" HPV infection status.

According to Dr. Ma, the team has plans to investigate which non-cancer-causing HPV types may play a role in cancers of the cervix, mouth and skin. The team also plans to develop better diagnostic tests, which would test for all known types of HPV.**Sperm cells are extremely efficient at swimming against a current: How sperm travel long distances, through difficult terrain, to reach an egg**

Like salmon traveling upstream to spawn, sperm cells are extremely efficient at swimming against the current, according to research to be published this week.

The discovery, to be published in the journal eLife by researchers at MIT and Cambridge University, may help us to understand how some sperm travel such long distances, through difficult terrain, to reach and fertilize an egg.

Of the hundreds of millions of sperm cells that begin the journey up the oviducts, only a few hardy travelers will ever reach their destination. Not only do the cells have to swim in the right direction over distances that are around 1,000 times their own length, but they are exposed to different chemicals and currents along the way.

While we know that sperm cells can "smell" chemicals given off by the egg once they get very close to it, this does not explain how they navigate for the majority of their journey, says Jörn Dunkel, an assistant professor of mathematics at MIT, and a member of the research team.

"We wanted to know which physical mechanisms could be responsible for navigation," says Dunkel, who carried out the research alongside Vasily Kantsler of the Skolkovo Institute of Science and Technology and the University of Warwick (and currently visiting at MIT); Raymond E. Goldstein of Cambridge; and Martyn Blayney of the Bourn Hall Clinic in the U.K. "If you think of salmon, for example, they can swim against the stream, and the question was whether something similar could really be confirmed for human sperm cells."

However, observing sperm cells swimming within the human body itself is no easy task. So in a bid to understand what the cells are capable of, the researchers instead built a series of artificial microchannels of different sizes and shapes, into which they inserted the sperm. They were then able to modify the flow of fluid through the tubes, to investigate how the cells responded to different current speeds.

They discovered that at certain flow speeds, the sperm cells were able to swim very efficiently upstream. "We found that if you create the right flow velocities, you can observe them swimming upstream for several minutes," Dunkel says. "The mechanism is very robust."

What's more, the researchers were also surprised to observe that the sperm were not swimming in a straight line upstream, but in a spiraling motion, along the walls of the channel. The sperm cells react to the difference in the speed of current near the walls of the chamber -- where the fluid is attracted to the surface, and is therefore at its slowest -- and the free-flowing center of the tube, Dunkel says.

If biologists are able to observe similar fluid-flow speeds within the oviduct, it could help confirm whether sperm cells are indeed using this mechanism to navigate through the body, he says. Not only would this improve our understanding of human reproduction, but it could also one day allow us to design new diagnostic tools and more efficient artificial-insemination techniques, the researchers claim. Reproduction specialists could take sperm samples and artificially recreate the conditions within the body to identify the cells that are the best swimmers, in a bid to preselect those most likely to succeed, Dunkel says.

The researchers can also experiment with different fluid viscosities within the microchannels, to determine which result in the strongest upstream swimming effect, he says. "So the idea would be to fine-tune the properties of the fluid medium that the sperm cells are contained in, before you insert it into the body, so that you know the cells can achieve optimal upstream swimming."

In the meantime, the researchers plan to begin investigating whether sperm cells can work together to reach the egg. "It is a commonly held belief that there is competition between sperm cells, with the fittest reaching the egg first," Dunkel says. "But recent studies by our team and others show that sperm practically always accumulate at the surface of a tube, and you can end up with a high local concentration of sperm cells, so there could actually be cooperation among these cells that allows them to swim faster collectively."

# If cells can't move, cancer can't grow

By blocking a widespread enzyme, Centenary researchers have shown they can slow down the movement of cells and potentially stop tumours from spreading and growing.

Using a new super-resolution microscope they’ve been able to see single molecules of the enzyme at work in a liver cancer cell line. Then they’ve used confocal microscopes to see how disrupting the enzyme slows down living cancer cells.

The enzyme is DPP9 (dipeptidyl peptidase 9) which the researchers at the Centenary Institute and the Sydney Medical School were first to discover and clone, in 1999. Ever since they’ve been studying what it does, with a view to its possible use as a cancer drug target.

“It was exciting to be able to watch the enzyme at work and then block DPP9, and see the cells slow down,” says A/Prof Mark Gorrell from Centenary’s Molecular Hepatology unit. “This gives us our clearest evidence yet that this enzyme will be a good cancer drug target.”

“What this work has shown us is that this enzyme is absolutely critical to cell movement, and without cell movement, tumors can’t grow or spread,” says Gorrell of the work, published in the the leading European cell biology journal BBA Molecular Cell Research.

Using the recently acquired super-resolution microscope, Ms Hui (Emma) Zhang—one of Gorrell’s PhD students— determined where individual fluorescently tagged DPP9 molecules were located inside cells. She found that DPP9 lies on the microtubules that play a significant role in intracellular transport and in cell migration.

When cells were stimulated to move, Zhang discovered DPP9 accumulates at the leading edge of the moving cell. DPP9 was also associated with the adhesion protein complex that glues the cell to the external matrix though which it moves, acting as an anchor point to pull the cell along. When the action of DPP9 was inhibited in cells, such movement and adhesion diminished.

“DPP9 is looking more and more like a cancer drug target. But at present we have no specific inhibitors for it, even though chemists have been trying for some years to make one.” he said. “We need to throw more resources at this problem.”

During the past 15 years, Gorrell has been unveiling the properties of DPP9, which belongs to a small family of four enzymes specialised in cleaving other proteins. Members of this family modify and regulate proteins for many important functions inside and outside of cells. DPP4, for instance, is already the basis of a leading drug treatment for diabetes. DPP4 inhibitors are worth about $6 billion a year and comprise about a quarter of the diabetes drug market.

“The roadblock to developing a specific inhibitor for DPP9 has been that it is very similar physically, but not functionally, to DPP8. It has been hard to distinguish between the two chemically,” Gorrell says. He is now working on determining and publishing differences between the two enzymes, which should help chemists target their efforts better.

# Microbial 'signature' for sexual crimes

Bacterial communities living on an individual's pubic hairs could be used as a microbial 'signature' to trace their involvement in sexual assault cases, according to a study published in the open access journal *Investigative Genetics*.

Hairs are one of the most common types of trace evidence collected during forensic investigations, but the majority of those recovered from crime scenes lack their roots and contain insufficient amounts of human genetic material to carry out DNA profiling of suspects.

To trace suspects from the hairs they leave at a crime scene, an alternative approach could be through the detection of a microbial 'signature'. Different areas of our bodies harbor distinct communities of microbe, or microbiota, but it is the significant differences between individual people's microbiota which may offer unique bacterial profiles for forensics.

In the first study of hair microbiota for forensics, researchers found in their preliminary results that pubic hairs in particular show the most potential for forensic investigations, with an ability to distinguish between males, females and individual people, based on the bacteria present. They also found that an individual's pubic hair microbiota appeared to be transferred during intercourse, suggesting its potential for forensic analysis on sexual assault cases.

Lead author Silvana Tridico from Murdoch University, Australia, said: "The advent of DNA profiling has resulted in an increase of sexual offenders using condoms, which they take away, post-assault. The implication of this present study is that the transfer of bacteria between victim and offender, in rape cases, may provide a new way of linking the offender to the victim, in instances in which no human DNA is transferred."

In the small study, seven individuals (three male and four female, two of whom were a co-habiting couple) each collected scalp and pubic hair samples at the start of the study. The researchers carried out an analysis of the hair samples to identify microbial DNA, in order to build a picture of the microbial communities which were present. This was repeated two and five months thereafter.

Scalp hair showed fewer distinct varieties of microbe (approximately 50 varieties in male hairs, and 55 in female) and appeared to be more influenced by common environmental microbes. In contrast, each individual's pubic hairs harboured distinct communities of microbe, with around 73 different varieties in male pubic hairs and 76 in females. The researchers say that these preliminary results suggest that microbial communities on pubic hairs could be used as microbial 'signatures' to identify individuals.

While the microbial communities on pubic hair generally remained individually distinct and consistent over the course of the study, in one instance at the five month time point, the co-habiting couple's microbiota were more similar to each other than previously. Interviewing revealed that the couple had sexual intercourse 18 hours prior to the collection of their pubic hairs. This suggests that an exchange of microbes had occurred which the researchers say bodes well for future forensic applications involving sexual crimes.

# Strategies identified to improve oral contraceptive success with obese women

The findings of a new study suggest two ways to effectively address the problem that birth control pills may not work as well in obese women, compared to women of a normal body mass index.

Birth control pills are a one-size-fits-all method, researchers say, but as the population has increased in weight, concern has grown about how well the pill works for obese women. Studies have consistently found that obesity has a negative impact on drug levels in the body, which may in turn affect how well the pill prevents pregnancy.

“Birth control pills have been shown in a large population study to fail at a higher rate in women who are obese,” said Ganesh Cherala, an assistant professor in the Oregon State University/Oregon Health & Science University College of Pharmacy.

“Our original studies were focused on why this might occur,” Cherala said, “and we found that obesity changes how a woman’s body clears contraceptive hormones.”

It takes longer for the pill to reach a steady state level in obese women, with possible impacts on efficacy of the birth control, and putting them at greater risk for a pill failure if they forget to take a pill or take it later.

In order to offset these changes, Cherala and Dr. Alison Edelman, an associate professor of obstetrics and gynecology at Oregon Health & Science University, studied two alternative strategies. They found that either a slight increase in the pill dose, from a very low dose to a low dose pill; or using the pill continuously without a “period week” off, appeared to counteract the changes that obesity causes.

This, in turn, may provide improved pregnancy prevention for women of differing weights who use the pill, the researchers said. Their work is published in Contraception, a professional journal, and was supported by the National Institutes of Health.

“Since oral contraception remains one of the most popular forms of birth control in the United States and the majority of our population is obese or overweight, it’s important to find methods of contraception that work for all women, no matter what their weight,” Edelman said.

“The strategies that we studied can be, and are currently being used by women, but now we know that they help to counteract the adverse effects of weight on contraceptive hormones,” she said.

For obese women, simply shifting to an alternative form of birth control is an option, the researchers said. But they also pointed out that oral contraceptives are the most preferred form of birth control and that a woman’s individual preference influences her adherence and continuation with any method.

# Parkinson's disease reverted at experimental stage

Mexican scientists demonstrated experimentally, with adult rats, that mobility can be restored in patients with Parkinson's disease, the major degenerative disease of the motor system worldwide. The experiments have not yet been transferred to humans, but are a scientific, measurable and repeatable basis to fight against this disease.

The Mexican study, led by Jorge Aceves Ruiz, an expert in physiology and emeritus researcher at the Center for Research and Advanced Studies (CINVESTAV), uses stem cells to generate a type of nerve cells known as dopaminergic and reactivate, orderly, the production of dopamine in the brain of rats with symptoms of shaking palsy or Parkinson's disease.

Aceves Ruiz's group has over 35 years of experience in research on brain physiology, but particularly in a region near the base in which the basal ganglia are located. In that area there are accumulations of nerve cells that make and release neurotransmitters such as dopamine. The treatment they have designed and tested in the laboratory uses stem cells that develop into dopamine producers or dopaminergic.

"Our treatment has allowed us to recover these motor impairments, which is associated with the recovery of neurons and dendritic spines of striatal neurons, which is the first thing that gets damaged in Parkinson's disease," explained Aceves Ruiz, who belongs to the permanent Seminar in Science and Technology of Mexico in the medical center "XXI Century" in Mexico City.

"We found that apparently the treatment by neurogenesis allows these newly formed neurons to be able to innervate, meaning that from stem cells present in the tissue itself, cell differentiation towards dopaminergic phenotype is induced."

After, at least four processes occur before regaining motor behavior: new dopaminergic cells send their terminals to the striatum, functionally reinnervate neurons, induce recovery of dendritic spines and recover the functionality of the cortical input, said the physiologist graduated from the National Autonomous University of Mexico (UNAM).

Until 35 years ago virtually nothing was known about the part of the brain called the basal ganglia, which are clusters of nerve cells at the base of the brain in which different molecules that help transmit messages between neurons are produced.

Following a period of study at the University of Cambridge, Aceves Ruiz met his Argentine colleague Claudio Cuello, with whom he began conducting experiments to see if they could produce dopamine by electrical stimuli. With trepidation he initiated a research path that has generated over 73 pioneering papers in pharmaceutical neurology.

"Now we know that, for example, basal ganglia are organized primarily in two ways: one that facilitates movement and one that inhibits it, under the action of dopamine," says Aceves.

"We know how the neurotransmitter works, and this has enabled us to design experiments that allow us to recover motor activity, we also determined through experiments that dopamine can promote or inhibit the movement under normal conditions; the problem is knowing when it promotes and when it stops, and to perform the process it uses different receptors."

Experiments with adult rats to give back control of movement continues, but also Mexican research has opened other fields of study on the action of dopamine and the consequences of its absence, for example, its effects on motor hyperactivity syndrome.

# Gene therapy cure for children with 'bubble baby' disease

UCLA stem cell researchers have pioneered a stem cell gene therapy cure for children born with adenosine deaminase (ADA)-deficient severe combined immunodeficiency (SCID), often called "Bubble Baby" disease, a life-threatening condition that if left untreated can be fatal within the first year of life.

The groundbreaking treatment was developed by renowned stem cell researcher and UCLA Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research member Dr. Donald Kohn, whose breakthrough was developed over three decades of research to create a gene therapy that safely restores immune systems in children with ADA-deficient SCID using the patient's own cells with no side effects. To date, 18 children with SCID have been cured of the disease after receiving the stem cell gene therapy in clinical trials at UCLA and the National Institutes of Health.

"All of the children with SCID that I have treated in these stem cell clinical trials would have died in a year or less without this gene therapy, instead they are all thriving with fully functioning immune systems" said Kohn, a professor of pediatrics and of microbiology, immunology and molecular genetics in Life Sciences.

To protect children born with SCID they are kept in isolation, in controlled environments because without an immune system they are extremely vulnerable to illness and infection that could be lethal.

Children born with SCID, an inherited immunodeficiency, are generally diagnosed at about six months. They are extremely vulnerable to infectious diseases, and in a child with ADA-deficient SCID even the common cold can prove fatal. The disease causes cells to not create an enzyme called ADA, which is critical for production of the healthy white blood cells that drive a normal, fully-functioning immune system. About 15 percent of all SCID patients are ADA-deficient.

Currently, the only treatments for these children include injecting them twice a week with the necessary enzyme, a life-long process that is very expensive and often doesn't return the immune system to optimal levels. These children also have the option to undergo bone marrow transplants from matched siblings, but matches are very rare or result in rejection of the transplanted cells which then turn against the child.

Since 2009 and over the course of a two multi-year clinical trials, Kohn and his team tested two therapy regimens on 18 children with ADA-deficient SCID. During the trials, the patient's blood stem cells were removed from their bone marrow and genetically modified to correct the defect. All of the 18 patients were cured.

Kohn used a virus delivery system that he first developed in his lab in the 1990s to insert the corrected gene that produces the missing enzyme necessary for a healthy immune system into the blood forming stem cells in the bone marrow. The genetically corrected blood forming stem cells then produce T cells that will fight infection.

He and colleagues tested different viral vectors, modifying each and perfecting viral delivery as the best method to put the healthy ADA genes back into the bone marrow cells of the patients. With the newly-transplanted cells now able to produce the needed enzyme, they use the powerful self-renewal potential of stem cells to repopulate the blood stream and the child develops their own new, fully-functioning immune system.

"We were very happy that over the course of several clinical trials and after making refinements and improvements to the treatment protocol, we are now able to provide a cure for babies with this devastating disease using the child's own cells," said Kohn. The next step is to seek FDA approval for the gene therapy in the hopes that all children with ADA-deficient SCID will be able to benefit from the treatment.

Only weeks after giving birth to fraternal twins in 2012, Alysia Padilla-Vacarro quickly felt something was wrong with one of her daughters, Evangelina, now two years old.

"I was told that it was the stress, or the fear of being a new mom, but I just knew something wasn't right," said Padilla-Vacarro. "Then I was informed that Evangelina had absolutely no immune system. That anything that could make her sick, would kill her. It was literally the worst time of my life."

Alysia and her husband Christian, of Corona, California, brought Evangelina to see Dr. Kohn at UCLA. Soon after undergoing Dr. Kohn's stem cell gene therapy treatment, Evangelina's new immune system developed without side effects. Her T cell count began to rise and her ability to fight off illness and infection grew stronger. Then Dr. Kohn told Alysia and Christian the good news. For the first time, they could hug and kiss their daughter and take Evangelina outside to meet the world.

"To finally kiss your child on the lips, to hold her, it's impossible to describe what a gift that is," Padilla-Vacarro said. "I gave birth to my daughter, but Dr. Kohn gave my baby life."

**Editing human germline cells sparks ethics debate**

Sci-fi novels and films like Gattaca no longer have a monopoly on genetically engineered humans. Real research scripts about editing the human genome are now appearing in scientific and medical journals. But the reviews are mixed. In Gattaca, nearly everyone was genetically altered, their DNA adjusted to prevent disease, enhance intelligence and make them look good. Today, only people treated with gene therapy have genetically engineered DNA. But powerful new gene editing tools could expand the scope of DNA alteration, forever changing humans' genetic destiny.

Not everyone thinks scientists should wield that power. Kindling the debate is a report by scientists from Sun Yat-sen University in Guangzhou, China, who have edited a gene in fertilized human eggs, called zygotes. The team used new gene editing technology known as the CRISPR/Cas9 system. That technology can precisely snip out a disease-causing mutation and replace it with healthy DNA. CRISPR/Cas9 has edited DNA in stem cells and cancer cells in humans. Researchers have also deployed the molecules to engineer other animals, including mice and monkeys. But it had never before been used to alter human embryos.

The team’s results sparked a flurry of headlines because their experiment modified human germline tissue. While most people think it is all right to fix faulty genes in mature body, or somatic, cells, tinkering with the germ line — eggs, sperm or tissues that produce those reproductive cells — crosses an ethical line for many. Germline changes can be passed on to future generations, and critics worry that allowing genetic engineering to correct diseases in germline tissues could pave the way for creating designer babies or other abuses that will persist forever.

“How do you draw a clear, meaningful line between therapy and enhancement?” ponders Marcy Darnovsky, executive director of the Center for Genetics and Society in Berkeley, Calif. About 40 countries ban or restrict such inherited DNA modifications.

Rumors about human germline editing experiments prompted scientists to gather in January in Napa, Calif. Discussions there led two groups to publish recommendations. One group called for scientists to “agree not to modify the DNA of human reproductive cells,” including the nonviable zygotes used in the Chinese study. A second group called for a moratorium on the clinical use of human germline engineering, but stopped short of saying the technology shouldn’t be used in research. Those researchers say that while CRISPR technology is still too primitive for safe use in patients, further research is needed to improve it. But other groups disagreed.

“Are there ever any therapeutic uses that would demand … modification of the human germ line? We don’t think there are any,” says Edward Lanphier, president of Sangamo BioSciences in Richmond, Calif. “Modifying the germ line is crossing the line that most countries on our planet have said is never appropriate to cross.”

If germline editing is never going to be allowed, there is no reason to conduct research using human embryos or reproductive cells, he says. Sangamo BioSciences is developing gene editing tools for use in somatic cells, an approach that germline editing might render unneeded. Lanphier denies that financial interests play a role in his objection to germline editing.

Other researchers, including Harvard University geneticist George Church, think germline editing may well be the only solution for some people with rare, inherited diseases. “What people want is safety and efficacy,” says Church. “If you ban experiments aimed at improving safety and efficacy, we’ll never get there.”

The zygote experiments certainly demonstrate that CRISPR technology is not ready for daily use yet. The researchers attempted to edit the beta globin, or *HBB*, gene. Mutations in that gene cause the inherited blood disorder beta-thalassemia. CRISPR/Cas9 molecules were engineered to seek out *HBB* and cut it where a piece of single-stranded DNA could heal the breach, creating a copy of the gene without mutations. That strategy succeeded in only four of the 86 embryos that the researchers attempted to edit. Those edited embryos contained a mix of cells, some with the gene edited and some without.

In an additional seven embryos, the *HBB* gene cut was repaired using the nearby *HBD* gene instead of the single-stranded DNA. The researchers also found that the molecular scissors snipped other genes that the researchers never intended to touch.

“Taken together, our work highlights the pressing need to further improve the fidelity and specificity of the CRISPR/Cas9 platform, a prerequisite for any clinical applications,” the researchers wrote.

Viable or not, germline cells should be off limits, says Darnovsky. She opposes all types of human germline modification. The U.K. prohibits all other germline editing. Such unproven technologies shouldn’t be attempted when alternatives already exist, Darnovsky says, such as screening embryos created through in vitro fertilization and discarding those likely to develop the disease.

But banning genome-altering technology could leave people with genetic diseases, and society in general, in the lurch, says molecular biologist Matthew Porteus of Stanford University.

“There is no benefit in my mind of having a child born with a devastating genetic disease,” he says. Alternatives to germline editing come with their own ethical quandaries, he says. Gene testing of embryos may require creating a dozen or more embryos before finding one that doesn’t carry the disease. The rest of the embryos would be destroyed. Many people find that prospect ethically questionable.

**Birth-weight boost tied to cleaner air during Beijing Olympics**

The Olympics are stuffed full of feel-good moments featuring amazing athletic feats, heart-warming backstories and national pride. Now, a new study details another Olympic win: Bigger babies.

Babies whose eighth month of gestation fell during the 2008 Beijing Olympics and Paralympics were born slightly heavier than babies born a year earlier or later. Why? Because those Olympic babies got a break from Beijing’s profoundly polluted air, [researchers suggest](http://ehp.niehs.nih.gov/1408795/) April 28 in *Environmental Health Perspectives.* The results serve as a stark reminder of how pollution can harm fetuses.

Olympic organizers in Beijing went to [great lengths](http://www.nytimes.com/2008/04/15/world/asia/15beijing.html) to clean up their air in advance of the 2008 Summer Games. The government took cars off roads, shuttered factories and even banned outdoor spray-painting. And those efforts worked. Concentrations of certain pollutants dropped.

Researchers led by epidemiologist David Rich of the University of Rochester Medical Center in New York realized that this rare break in pollution was a golden opportunity to study the effects of dirty air on pregnancy.

The team combed through health records of more than 80,000 pregnant women in Beijing to see whether the pollution drop had any effect on the outcome. Women whose eighth month of pregnancy coincided with the Olympics went on to have babies who were an average of 23 grams heavier than the babies of women whose eighth month of pregnancy came the year before or after, the researchers found.

That average birth weight may have responded to such a short bout of clean air makes you wonder what pollution is doing to fetuses who experience it for all 40 weeks. “Even in this 47-day period you see a public health benefit like this,” Rich says. “Imagine what you could do if you could have air pollution levels reduced throughout the whole entire pregnancy.”

The timing of the pregnancy seemed to matter. The researchers found that baby weight went up when clearer skies coincided with the eighth month of pregnancy, a time when a fetus is really packing on pounds. Finding an effect there “makes a lot of sense,” says epidemiologist Beate Ritz of the University of California, Los Angeles, who wasn’t involved in the study.

Twenty-three grams — about 0.8 ounces — isn’t a big difference. In fact, it’s less than 1 percent of these babies’ median weight. But that slight change may serve as a bellwether for more insidious effects.

“It’s really important, not so much as ‘Oh, those few grams, do they really matter in the life of this child?’’ Ritz says. “That’s not really what we’re asking.” Instead, scientists suspect that if pollution is behind the weight difference, then dirty skies could be inflicting damage on other developing organs and systems too. Pollution during pregnancy could be programming these babies to develop in a way that leads to important differences in the immune system, the brain and other systems, she says.

It’s also possible that pollution might do more damage earlier in pregnancy, Ritz says. Dirty air could be contributing to early miscarriages, which would be hard to study.

More research is needed to figure out just how the pollution may be affecting fetuses, and babies, and people for that matter. But what people really need is more than just a temporary reprieve from pollution.

**Major advance in artificial photosynthesis poses win/win for the environment**

By combining biocompatible light-capturing nanowire arrays with select bacterial populations, a potentially game-changing new artificial photosynthesis system offers a win/win situation for the environment: solar-powered green chemistry using sequestered carbon dioxide.

A potentially game-changing breakthrough in artificial photosynthesis has been achieved with the development of a system that can capture carbon dioxide emissions before they are vented into the atmosphere and then, powered by solar energy, convert that carbon dioxide into valuable chemical products, including biodegradable plastics, pharmaceutical drugs and even liquid fuels.

Scientists with the U.S. Department of Energy (DOE)'s Lawrence Berkeley National Laboratory (Berkeley Lab) and the University of California (UC) Berkeley have created a hybrid system of semiconducting nanowires and bacteria that mimics the natural photosynthetic process by which plants use the energy in sunlight to synthesize carbohydrates from carbon dioxide and water. However, this new artificial photosynthetic system synthesizes the combination of carbon dioxide and water into acetate, the most common building block today for biosynthesis.

"We believe our system is a revolutionary leap forward in the field of artificial photosynthesis," says Peidong Yang, a chemist with Berkeley Lab's Materials Sciences Division and one of the leaders of this study. "Our system has the potential to fundamentally change the chemical and oil industry in that we can produce chemicals and fuels in a totally renewable way, rather than extracting them from deep below the ground."

The more carbon dioxide that is released into the atmosphere the warmer the atmosphere becomes. Atmospheric carbon dioxide is now at its highest level in at least three million years, primarily as a result of the burning of fossil fuels. Yet fossil fuels, especially coal, will remain a significant source of energy to meet human needs for the foreseeable future. Technologies for sequestering carbon before it escapes into the atmosphere are being pursued but all require the captured carbon to be stored, a requirement that comes with its own environmental challenges. The artificial photosynthetic technique developed by the Berkeley researchers solves the storage problem by putting the captured carbon dioxide to good use.

"In natural photosynthesis, leaves harvest solar energy and carbon dioxide is reduced and combined with water for the synthesis of molecular products that form biomass," says Chris Chang, an expert in catalysts for carbon-neutral energy conversions. "In our system, nanowires harvest solar energy and deliver electrons to bacteria, where carbon dioxide is reduced and combined with water for the synthesis of a variety of targeted, value-added chemical products."

"Our system represents an emerging alliance between the fields of materials sciences and biology, where opportunities to make new functional devices can mix and match components of each discipline," says Michelle Chang, an expert in biosynthesis. "For example, the morphology of the nanowire array protects the bacteria like Easter eggs buried in tall grass so that these usually-oxygen sensitive organisms can survive in environmental carbon-dioxide sources such as flue gases."

"Our artificial forest is similar to the chloroplasts in green plants," Yang says. "When sunlight is absorbed, photo-excited electron pairs are generated in the silicon and titanium oxide nanowires, which absorb different regions of the solar spectrum. The photo-generated electrons in the silicon will be passed onto bacteria for the CO2 reduction while the photo-generated holes in the titanium oxide split water molecules to make oxygen."

Once the forest of nanowire arrays is established, it is populated with microbial populations that produce enzymes known to selectively catalyze the reduction of carbon dioxide. For this study, the Berkeley team used Sporomusa ovata, an anaerobic bacterium that readily accepts electrons directly from the surrounding environment and uses them to reduce carbon dioxide.

"*S. ovata* is a great carbon dioxide catalyst as it makes acetate, a versatile chemical intermediate that can be used to manufacture a diverse array of useful chemicals," says Michelle Chang. "We were able to uniformly populate our nanowire array with *S. ovata* using buffered brackish water with trace vitamins as the only organic component."

Once the carbon dioxide has been reduced by *S. ovata* to acetate (or some other biosynthetic intermediate), genetically engineered E.coli are used to synthesize targeted chemical products. To improve the yields of targeted chemical products, the *S. ovata* and E.coli were kept separate for this study. In the future, these two activities -- catalyzing and synthesizing -- could be combined into a single step process.

A key to the success of their artificial photosynthesis system is the separation of the demanding requirements for light-capture efficiency and catalytic activity that is made possible by the nanowire/bacteria hybrid technology. With this approach, the Berkeley team achieved a solar energy conversion efficiency of up to 0.38-percent for about 200 hours under simulated sunlight, which is about the same as that of a leaf.

The yields of target chemical molecules produced from the acetate were also encouraging -- as high as 26-percent for butanol, a fuel comparable to gasoline, 25-percent for amorphadiene, a precursor to the antimaleria drug artemisinin, and 52-percent for the renewable and biodegradable plastic PHB. Improved performances are anticipated with further refinements of the technology.

"We are currently working on our second generation system which has a solar-to-chemical conversion efficiency of three-percent," Yang says. "Once we can reach a conversion efficiency of 10-percent in a cost effective manner, the technology should be commercially viable."