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# Researchers Alter Mosquito Genome With Goal of Controlling Disease

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Virginia Tech researchers successfully used a gene disruption technique to change the eye color of a mosquito -- a critical step toward new genetic strategies aimed at disrupting the transmission of diseases such as dengue fever. The varied colors of the eyes of these mosquitoes, modified using TALEN technology, is because of cell-to-cell variability in the degree of gene editing. (Credit: Virginia Tech)

Mar. 21, 2013 — Virginia Tech researchers successfully used a gene disruption technique to change the eye color of a mosquito -- a critical step toward new genetic strategies aimed at disrupting the transmission of diseases such as dengue fever.

Zach Adelman and Kevin Myles, both associate professors of entomology in the College of Agriculture and Life Sciences and affiliated researchers with the Fralin Life Science Institute, study the transmission of vector-borne diseases and develop novel methods of control, based on genetics.

In a groundbreaking study published this week in the journal PLOS One, the scientists used a pair of engineered proteins to cut DNA in a site-specific manner to disrupt a targeted gene in the mosquito genome. Science magazine heralded these transcription activator-like effector nuclease proteins, known as TALENS, as a major scientific breakthrough in 2012, nicknaming them "genomic cruise missiles" for their ability to allow researchers to target specific locations with great efficiency.

While TALENS have been previously used to edit the genomes of animal and human cell cultures, applying them to the mosquito genome is a new approach, according to Adelman.

"Unlike model organisms with large collections of mutant strains to draw upon, the lack of reverse genetic tools in the mosquito has made it is very difficult to assign functions to genes in a definitive manner," Adelman said. "With the development of this technology, our understanding of the genetic basis of many critical behaviors such as blood-feeding, host-seeking and pathogen transmission should be greatly accelerated."

To test the capability of TALENs to specifically edit the mosquito genome, the scientists designed a pair of TALENS to target a gene whose protein product is essential to the production of eye pigmentation in Aedes aegypti, a mosquito species known for its transmission of the viruses that cause dengue fever.

Using the TALEN pair to edit the gene in the mosquito's germ cells early in development, they were able to change the eye color of a large percentage of the mosquitoes arising in the next generation from black to white.

"To date, efforts to control dengue transmission through genetics have focused entirely on adding material to the mosquito genome. Ensuring that this added material is expressed properly and consistently has been a challenge," Adelman said. "This technology allows us to pursue the same goals, namely, the generation of pathogen-resistant mosquitoes, through subtraction. For example, removing or altering a gene that is critical for pathogen replication."

"Aedes mosquitoes have become increasingly important as vectors of disease from a public health perspective," said George Dimopoulos, a professor of molecular microbiology and immunology at John Hopkins University who was not involved in the study. "The lack of vaccines and drugs for dengue has left the mosquitoes that carry the virus as one of the most promising targets for controlling the disease. A better understanding of how the virus infects the mosquito and other biological properties of the insect will be required to develop intervention strategies that can block virus transmission by the mosquito. The ability to genetically engineer mosquitoes is essential for the study of such biological functions. The TALEN-based system in mosquitoes that that was developed by Dr. Adelman provides this important capacity."

Co-authors of the study include Azadeh Aryan, a Ph.D. student in the department of entomology in the College of Agriculture and Life Sciences, and Michelle A.E. Anderson, a research technician in the department of entomology in the College of Agriculture and Life Sciences.

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# Indirect Side-Effects of the Cultivation of Genetically Modified Plants

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Let's eat: a caterpillar of the species Heliothis virescens on a cotton leaf. (Credit: © Lawo Nora, Agroscope ART)

Mar. 13, 2013 — Genetically modified Bt cotton plants contain a poison that protects them from their most significant enemies. As a result, these plants rely less on their own defence system. This benefits other pests, such as aphids. These insights stem from a study supported by the Swiss National Science Foundation (SNSF).

Just ten years ago, genetically modified cotton grew on 12% of all fields -- today it is cultivated on over 80% of all cotton fields around the world. Bt cotton contains a gene of Bacillus thuringiensis, a species of soil bacteria. The plant uses it to produce a poison whose effects are fatal to the principal cotton pests -- voracious caterpillars. However, certain types of bugs and other pests begin to spread across cotton fields instead, as is the case in China. The decline in the use of chemical pesticides may be partly responsible for this development, but it is probably not the only factor.

**Spoiling their appetites**

A team of researchers led by Jörg Romeis from the Agroscope Reckenholz-Tänikon Research Station has now identified a biological mechanism that offers an additional explanation for the increase in new pests in Bt cotton fields. Cotton plants have a sophisticated defence system. When caterpillars begin to nibble on them, they form defensive substances, so-called terpenoids. This spoils the appetite of not only the caterpillars, but of many other nibblers as well.

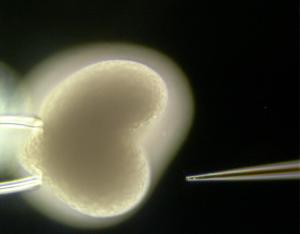
**Also helpful against bugs?**

Cotton aphids generally do not cause severe agricultural damage because they succumb to their natural enemies out in the open. His results are therefore not relevant to farming, says Romeis. However, he has for the first time revealed an indirect effect of Bt cotton: the killing of the caterpillars also affects other plant-eating insects because the plants' defence system remains inactive. Romeis now wants to investigate whether this effect is relevant to aphids only or also to the bugs that are creating problems for cotton farmers in China and in other cotton-growing regions of the world.

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# Solving the Mystery of Aging: Longevity Gene Makes Hydra Immortal and Humans Grow Older

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A gene sequence is injected into an embryo of Hydra. (Credit: Copyright CAU/Wittlieb)

Nov. 13, 2012 — Why do we get older? When do we die and why? Is there a life without aging? For centuries, science has been fascinated by these questions. Now researchers from Kiel (Germany) have examined why the polyp Hydra is immortal -- and unexpectedly discovered a link to aging in humans.

The study carried out by Kiel University together with the University Medical Center Schleswig-Holstein (UKSH) will be published this week in the Proceedings of the National Academy of Sciences (PNAS).

**Hydra -- mysteriously immortal**

The tiny freshwater polyp Hydra does not show any signs of aging and is potentially immortal. There is a rather simple biological explanation for this: these animals exclusively reproduce by budding rather than by mating. A prerequisite for such vegetative-only reproduction is that each polyp contains stem cells capable of continuous proliferation. Without these stem cells, the animals could not reproduce any more. Due to its immortality, Hydra has been the subject of many studies regarding aging processes for several years.

**Aging in humans**

When people get older, more and more of their stem cells lose the ability to proliferate and thus to form new cells. aging tissue cannot regenerate any more, which is why for example muscles decline. Elderly people tend to feel weaker because their heart muscles are affected by this aging process as well. If it were possible to influence these aging processes, humans could feel physically better for much longer. Studying animal tissue such as those of Hydra -- an animal full of active stem cells during all its life -- may deliver valuable insight into stem cell aging as such.

**Human longevity gene discovered in Hydra**

"Surprisingly, our search for the gene that causes Hydra to be immortal led us to the so-called FoxO gene," says Anna-Marei Böhm, PhD student and first author of the study. The FoxO gene exists in all animals and humans and has been known for years. However, until now it was not known why human stem cells become fewer and inactive with increasing age, which biochemical mechanisms are involved and if FoxO played a role in aging. In order to find the gene, the research group isolated Hydra's stem cells and then screened all of their genes.

**Immortality mechanism of Hydra revealed**

The Kiel research team examined FoxO in several genetically modified polyps: Hydra with normal FoxO, with inactive FoxO and with enhanced FoxO. The scientists were able to show that animals without FoxO possess significantly fewer stem cells. Interestingly, the immune system in animals with inactive FoxO also changes drastically. "Drastic changes of the immune system similar to those observed in Hydra are also known from elderly humans," explains Philip Rosenstiel of the Institute of Clinical Molecular Biology at UKSH, whose research group contributed to the study.

**FoxO makes human life longer, too**

"Our research group demonstrated for the first time that there is a direct link between the FoxO gene and aging," says Thomas Bosch from the Zoological Institute of Kiel University, who led the Hydra study. Bosch continues: "FoxO has been found to be particularly active in centenarians -- people older than one hundred years -- which is why we believe that FoxO plays a key role in aging -- not only in Hydra but also in humans." However, the hypothesis cannot be verified on humans, as this would require a genetic manipulation of humans. Bosch stresses however that the current results are still a big step forward in explaining how humans age. Therefore the next step must be to study how the longevity gene FoxO works in Hydra, and how environmental factors influence FoxO activity.

**Without stem cells we all die**

Scientifically, the study has two major conclusions: On the one hand it confirms that the FoxO gene plays a decisive role in the maintenance of stem cells. It thus determines the life span of animals -- from cnidarians to humans. On the other hand, the study shows that aging and longevity of organisms really depend on two factors: the maintenance of stem cells and the maintenance of a functioning immune system.

This work was funded by the German Research Foundation DFG.

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# New Brain Gene Gives Us Edge Over Apes, Study Suggests

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Silverback gorilla. Scientists have taken a step forward in helping to solve one of life's greatest mysteries -- what makes us human? (Credit: © Maridav / Fotolia)

Nov. 14, 2012 — Scientists have taken a step forward in helping to solve one of life's greatest mysteries -- what makes us human? An international team of researchers have discovered a new gene that helps explain how humans evolved from chimp-like ancestors.

Scientists say the gene -- called miR-941 -- appears to have played a crucial role in human brain development and may shed light on how we learned to use tools and language.

Researchers say it is the first time that a new gene -- carried only by humans and not by apes -- has been shown to have a specific function within the human body.

A team at the University of Edinburgh compared the human genome to 11 other species of mammals, including chimpanzees, gorillas, mouse and rat, to find the differences between them.

The results, published in Nature Communications, showed that the gene -- miR-941 -- is unique to humans. The researchers say that it emerged between six and one million years ago, after humans had evolved from apes.

The gene is highly active in two areas of the brain that control our decision making and language abilities. The study suggests it could have a role in the advanced brain functions that make us human.

It is known that most differences between species occur as a result of changes to existing genes, or the duplication and deletion of genes.

But scientists say this gene emerged fully functional out of non-coding genetic material, previously termed "junk DNA," in a startlingly brief interval of evolutionary time. Until now, it has been remarkably difficult to see this process in action.

Researcher Dr Martin Taylor, who led the study at the Institute of Genetics and Molecular Medicine at the University of Edinburgh, said the results were significant.

He said: "As a species, humans are wonderfully inventive -- we are socially and technologically evolving all the time. But this research shows that we are innovating at a genetic level too. This new molecule sprang from nowhere at a time when our species was undergoing dramatic changes: living longer, walking upright, learning how to use tools and how to communicate. We're now hopeful that we will find more new genes that help show what makes us human."

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# Humans, Chimpanzees and Monkeys Share DNA but Not Gene Regulatory Mechanisms



Chimpanzee. Humans share over 90% of their DNA with their primate cousins. The expression or activity patterns of genes differ across species in ways that help explain each species' distinct biology and behavior. (Credit: © davemhuntphoto / Fotolia)

Nov. 6, 2012 — Humans share over 90% of their DNA with their primate cousins. The expression or activity patterns of genes differ across species in ways that help explain each species' distinct biology and behavior.

DNA factors that contribute to the differences were described on Nov. 6 at the American Society of Human Genetics 2012 meeting in a presentation by Yoav Gilad, Ph.D., associate professor of human genetics at the University of Chicago.

Dr. Gilad reported that up to 40% of the differences in the expression or activity patterns of genes between humans, chimpanzees and rhesus monkeys can be explained by regulatory mechanisms that determine whether and how a gene's recipe for a protein is transcribed to the RNA molecule that carries the recipe instructions to the sites in cells where proteins are manufactured.

In addition to improving scientific understanding of the uniqueness of humans, studies such as the investigation conducted by Dr. Gilad and colleagues could have relevance to human health and disease.

"Through inter-species' comparisons at the DNA sequence and expression levels, we hope to identify the genetic basis of human specific traits and in particular the genetic variations underlying the higher susceptibility to certain diseases such as malaria and cancer in humans than in non-human primates," said Dr. Gilad.

Dr. Gilad and his colleagues studied gene expression in lymphoblastoid cell lines, laboratory cultures of immortalized white blood cells, from eight humans, eight chimpanzees and eight rhesus monkeys.

They found that the distinct gene expression patterns of the three species can be explained by corresponding changes in genetic and epigenetic regulatory mechanisms that determine when and how a gene's DNA code is transcribed to a messenger RNA (mRNA) molecule.

Dr. Gilad also determined that the epigenetics process known as histone modification also differs in the three species. The presence of histone marks during gene transcription indicates that the process is being prevented or modified.

"These data allowed us to identify both conserved and species-specific enhancer and repressor regulatory elements, as well as characterize similarities and differences across species in transcription factor binding to these regulatory elements," Dr. Gilad said.

Among the similarities among the three species were the promoter regions of DNA that initiated transcription of a particular gene.

In all three species, Dr. Gilad's lab found that transcription factor binding and histone modifications were identical in over 67% of regulatory elements in DNA segments that are regarded as promoter regions.

The researchers presentation is titled, "Genome-wide comparison of genetic and epigenetic regulatory mechanisms in primates."

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# "Mighty Mouse" Gene Works The Same Way In People

June 24, 2004 — By studying the genes of a German child born with unusually well developed muscles, an international research team has discovered the first evidence that the gene whose loss makes "mighty mice" also controls muscle growth in people.

Writing in the June 24 issue of the New England Journal of Medicine, German neurologist Markus Schuelke, M.D., and the team show that the child's extra-large muscles are due to an inherited mutation that effectively silences the myostatin gene, proving that its protein normally keeps muscle development in check in people.

People with muscle-wasting conditions such as muscular dystrophy, and others just wanting to "bulk up," have eagerly followed work on myostatin, hoping for a way to counteract the protein's effects in order to build or rebuild muscle mass. But while research with mice has continued to reveal myostatin's role and the effects of interfering with it, no one knew whether any of the results would be relevant to humans.

"This is the first evidence that myostatin regulates muscle mass in people as it does in other animals," says Se-Jin Lee, M.D., Ph.D., professor of molecular biology and genetics in the Institute for Basic Biomedical Sciences at Johns Hopkins and co-author on the study. "That gives us a great deal of hope that agents already known to block myostatin activity in mice may be able to increase muscle mass in humans, too."

Lee and his team discovered in 1997 that knocking out the myostatin gene led to mice that were twice as muscular as their normal siblings, lending them the moniker "mighty mice." Later, others showed that naturally bulky cattle, such as Belgian Blues, got their extra muscles from lack of myostatin, too.

An unusual opportunity to examine myostatin's role in humans arose when Schuelke examined a newborn baby boy, almost five years ago, and was struck by the visible muscles on the infant's upper legs and upper arms. When ultrasound proved that the muscles were roughly twice as large as other infants', but otherwise normal, Schuelke realized that a naturally occurring mutation in the child's myostatin gene might be the cause.

Sequencing the myostatin gene from the boy and his mother, who had been a professional athlete, revealed a single change in the building blocks of the gene's DNA. Surprisingly, the change was not in the gene regions that correspond to the resulting protein, but in the intervening regions that are used only to create protein-making instructions, thus changing the gene's protein-building message.

"The mutation caused the gene's message, the messenger RNA, to be wrong," says Hopkins neurologist Kathryn Wagner, M.D., Ph.D., who tested the genetic mutation's effect in laboratory studies. "If the message had been used to make a protein, it would be much shorter than it should be. But we think the process doesn't even get that far; instead the cells just destroy the message."

Co-authors from Wyeth Research, Cambridge, Mass., analyzed samples of the child's blood for evidence of the myostatin protein and found none. "Both copies of the child's myostatin gene have this mutation, so little if any of the myostatin protein is made," says Schuelke. "As a result, he has about twice the muscle mass of other children."

Completely lacking myostatin, the boy is stronger than other children his age, and fortunately has no signs of problems with his heart so far, Schuelke says. But he adds that it's impossible to know whether the lack of myostatin in that crucial muscle might lead to problems as the boy gets older.

While other family members -- the boy's mother and her brother, father and grandfather -- were also reported to have been usually strong, only the mother's DNA was available for analysis along with her son's. Schuelke discovered that only one copy of the mother's myostatin gene had the mutation found in both copies of her son's myostatin gene. (We have two copies of each gene; one inherited from the mother and one inherited from the father.)

The Johns Hopkins researchers were funded by the National Institutes of Health and the Muscular Dystrophy Association. The German researchers were funded by the parents' self-help group (Helft dem muskelkranken Kind).

Authors on the paper are Schuekle, Christoph Hubner, Thomas Riebel and Wolfgang Komen of Charite, University Medical Center Berlin, Germany; Wagner and Lee of Johns Hopkins; Leslie Stolz and James Tobin of Wyeth Research, Cambridge, Ma.; and Thomas Braun of Martin-Luther-University, Halle-Wittenberg, Germany.

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# Zinc Fingers: A New Tool in the Fight Against Huntington's Disease

Oct. 10, 2012 — Huntington's disease (HD) is an inherited genetic disorder caused by the multiple repetition of a DNA sequence (the nucleotides CAG) in the gene encoding a protein called "Huntingtin". People who do not suffer from the disease have this sequence repeated 10 to 29 times. But in an affected person, the triplet is present more than 35 times.

Huntingtin protein can be found in various tissues of the human body and is essential for the development and survival of neurons in adults. When the mutant gene is present, an aberrant form of the Hungtingtin protein is produced, causing the symptoms of the disease: involuntary movements, changes in behavior and dementia, among others. Although there are several promising studies, there is currently no cure for HD. There are only palliative treatments of symptoms, and Huntington's patients die about 15 years after the symptoms onset.

Unlike other neurodegenerative diseases (such as Alzheimer or Parkinson), only a single gene is responsible for HD (i.e. the disorders is monogenic), and a therapy based on the inhibition of the gene, will open new perspectives of research for the development of a treatment.

A recently developed tool by scientists around the world is based on the modification of proteins that are found naturally in all living beings. These proteins are called Zinc Finger proteins, and can recognize and bind to specific DNA sequences. This enables the regulation of those genes to which they are attached.

A study conducted by researchers of the Centre for Genomic Regulation (CRG) in Barcelona provides positive results reducing the chromosomal expression of the mutant gene, which would prevent the development of disease. The research is published in Early Edition by the journal Proceedings of the National Academy of Sciences (PNAS).

"We designed specific ZFP that recognize and specifically bind to more than 35 repetitions of CAG triplet, preventing the expression of the gene containing these repeats and reducing the production of the mutant Huntingtin protein. When applying this treatment to a transgenic mouse model carrying the human mutant Huntingtin gene, we observed a delayed onset of the symptoms, "says Mireia Garriga-Canut, first author of the study and researcher at the Gene Network Engineering group at the CRG. Another co-author of the study, Carmen Agustín Pavón, adds that "the next step is to optimize the design for an effective and durable treatment for patients. This would pave the way to find a therapy for Huntington's disease".

The research was funded by the FP7 program of the European Commission and the Ministry of Science and Innovation of Spain.

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# Genetically Engineered Tomatoes Decrease Plaque Build-Up in Mice

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For the first time, researchers have genetically engineered tomato plants to produce a peptide that mimics the actions of good cholesterol when eaten. (Credit: © dr\_ox / Fotolia)

Nov. 5, 2012 — For the first time, genetically engineered tomato plants produced a peptide that mimics the actions of good cholesterol when eaten, researchers reported at the American Heart Association's Scientific Sessions 2012.

In the study, mice that ate the freeze-dried, ground tomatoes had less inflammation and reduced atherosclerosis (plaque build-up in the arteries).

"We have found a new and practical way to make a peptide that acts like the main protein in good cholesterol, but is many times more effective and can be delivered by eating the plant," said Alan M. Fogelman, M.D., senior author of the study and executive chair of the Department of Medicine and director of the Atherosclerosis Research Unit in the David Geffen School of Medicine at UCLA.

Researchers genetically engineered the tomatoes to produce 6F, a small peptide that mimics the action of ApoA-1, the chief protein in high density lipoprotein (HDL or "good" cholesterol). They fed the tomatoes to mice that lack the ability to remove low density lipoprotein (LDL or "bad" cholesterol) from their blood and readily develop inflammation and atherosclerosis when consuming a high-fat diet.

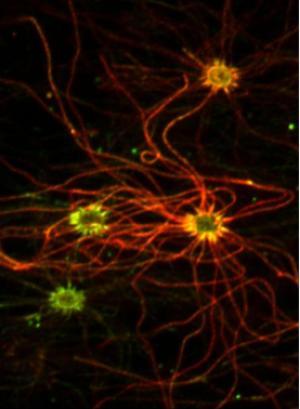
After the mice ate the tomatoes as 2.2 percent of their Western-style high-fat, calorie-packed diet, those given the peptide-enhanced tomatoes had significantly:

* lower blood levels of inflammation;
* higher paraoxonase activity, an anti-oxidant enzyme associated with good cholesterol and related to a lower risk of heart disease;
* higher levels of good cholesterol;
* decreased lysophosphatidic acid, a tumor promoter that accelerates plaque build-up in arteries in animal models; and
* less atherosclerotic plaque.

"To our knowledge this is the first example of a drug with these properties that has been produced in an edible plant and is biologically active when fed without any isolation or purification of the drug," Fogelman said.

Co-authors are Arnab Chattopadhyay, Ph.D.; Mohamad Navab, Ph.D.; Greg Hough, B.S.; David Meriwether, B.S.; Gao Feng, Ph.D.; Victor Grijalva, B.S.; James R. Springstead, Ph.D.; Mayakonda N. Palgunachari, Ph.D.; Ryan Namiri-Kalantari, B.S.; G.M. Anantharamaya, Ph.D.; Robin Farias-Eisner, M.D., Ph.D.; and Srinivasa T. Reddy, Ph.D. Author disclosures are on the abstract.

The National Heart, Lung, and Blood Institute funded the study.



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# Can’t Smell Anything? Discovery May Give You Hope

A microscopic view of cells that detect odors (olfactory sensory neurons) with yellow and green stains showing cilia. (Credit: Image courtesy of University of Michigan Health System)

Sep. 2, 2012 — Scientists have restored the sense of smell in mice through gene therapy for the first time -- a hopeful sign for people who can't smell anything from birth or lose it due to disease.

The achievement in curing congenital anosmia -- the medical term for lifelong inability to detect odors -- may also aid research on other conditions that also stem from problems with the cilia. Those tiny hair-shaped structures on the surfaces of cells throughout the body are involved in many diseases, from the kidneys to the eyes.

The new findings, published online in Nature Medicine, come from a team at the University of Michigan Medical School and their colleagues at several other institutions.

The researchers caution that it will take time for their work to affect human treatment, and that it will be most important for people who have lost their sense of smell due to a genetic disorder, rather than those who lose it due to aging, head trauma, or chronic sinus problems. But their work paves the way for a better understanding of anosmia at the cellular level.

"Using gene therapy in a mouse model of cilia dysfunction, we were able to rescue and restore olfactory function, or sense of smell," says senior author Jeffrey Martens, Ph.D., an associate professor of pharmacology at U-M. "Essentially, we induced the neurons that transmit the sense of smell to regrow the cilia they'd lost."

The mice in the study all had a severe genetic defect that affected a protein called IFT88, causing a lack of cilia throughout their bodies. Such mice are prone to poor feeding and to early death as a result. In humans, the same genetic defect is fatal.

The researchers were able to insert normal IFT88 genes into the cells of the mice by giving them a common cold virus loaded with the normal DNA sequence, and allowing the virus to infect them and insert the DNA into the mouse's own cells. They then monitored cilia growth, feeding habits, and well as signals within and between the nerve cells, called neurons, that are involved in the sense of smell.

Only 14 days after the three-day treatment, the mice had a 60 percent increase in their body weight, an indication they were likely eating more. Cell-level indicators showed that neurons involved in smelling were firing correctly when the mice were exposed to amyl acetate, a strong-smelling chemical also called banana oil.

"At the molecular level, function that had been absent was restored," says Martens.

"By restoring the protein back into the olfactory neurons, we could give the cell the ability to regrow and extend cilia off the dendrite knob, which is what the olfactory neuron needs to detect odorants," says postdoctoral fellow and first author Jeremy McIntyre, Ph.D.

Martens notes that the research has importance for other ciliopathies, or diseases caused by cilia dysfunction. These include such conditions as polycystic kidney disease, retinitis pigmentosa in the eye, and rare inherited disorders such as Alström syndrome, Bardet-Biedl syndrome, primary ciliary dyskinesia and nephronopthisis.

Scientists believe that nearly every cell in the body has the capacity to grow one or more cilia. In the olfactory system, multiple cilia project from olfactory sensory neurons, sensory cells that are found in the olfactory epithelium, tissue high up in the nasal cavity. Receptors that bind odorants are localized on the cilia, which is why a loss of cilia results in a loss in the ability to smell.

Because the new findings show that gene therapy is a viable option for the functional rescue of cilia in established, already differentiated cells, researchers working on those conditions might be able to use gene therapy to attempt to restore cilia function as well.

Meanwhile, Martens and his team will continue to look for other cilia-related genetic causes of anosmia, including those that are not lethal in humans.

"We hope this stimulates the olfactory research community to look at anosmia caused by other factors, such as head trauma and degenerative diseases," he says. "We know a lot about how this system works -- now have to look at how to fix it when it malfunctions." And, he notes because the neurons involved in the sense of smell connect to the nose, delivery of gene therapy treatments would not need to involve invasive procedures.

The study was funded by four parts of National Institutes of Health: the National Institute on Deafness and Other Communications Disorders, the National Institute on Diabetes and Digestive and Kidney Diseases, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, and the National Eye Institute.

In addition to Martens and McIntyre, the paper's authors include Ariell Joiner, Corey Williams, Paul Jenkins, Dyke McEwen, Lian Zhang and John Escobado from the Martens lab at U-M; Randall Reed from the Johns Hopkins University; Erica Davis, I-Chun Tsai and Nicholas Katsanis from Duke University; Aniko Sabo, Donna Muzny and Richard Gibbs from the Baylor College of Medcine; Eric Green and James Mullikin from the National Institutes of Health Intramural Sequencing Center; Bradley Yoder from the University of Alabama-Birmingham; Sophie Thomas and Tania Attié-Bitach from the Université Paris Descartes; Katarzyna Szymanska and Colin A Johnson from St. James's University Hospital in Leeds, UK; and Philip Beales from University College London, UK.

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# Gene Causes Blue Light to Have a Banana Odor in Fruit Flies

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Petri dish with fly larvae, irradiated with blue light from underneath. Unchanged larvae normally avoid areas exposed to light. The light has a pleasant odor for the modified larvae thus they move towards it. Larvae that appear to be white are discernible on the illuminated surface. (Credit: Image courtesy of Ruhr-Universitaet-Bochum)

May 26, 2010 — Scientists at Germany's Ruhr-Universitaet-Bochum have succeeded to genetically modify Drosophila (fruit fly) larvae allowing them to smell blue light.

The research team can activate single receptor neurons out of 28 olfactory neurons in the larvae for this sensory perception. Normally animals avoid light. However, blue light simulates in genetically modified larvae the smell of an odorant, e.g., banana, marzipan or glue -- odors which are all present in rotting fruit and attractive to fruit fly larvae. The team of scientists from Bochum and Göttingen, working under the auspices of Prof. Klemens Störtkuhl, hopes to gain insight into the processing of the neural network. They have published their findings in the journal Frontiers in Neuroscience Behavior.

**Light has a “tasty” odor**

The olfactory neurons of the only one millimeter sized genetically modified Drosophila larvae are all capable of producing the protein that is activated by light. The researchers can freely select which of the 28 cells will ultimately be light-sensitive using genetic markers. Prof. Störtkuhl explained that they were able to either activate cells which normally register repulsive odors and subsequently cause an aversion response, or cells that sense attractive odors such as banana, marzipan or glue. The activated neurons send an electrical signal if they are stimulated with blue light at a wavelength of 480 nm. The larva thus has the impression that it perceives odors. The experiment shows that it is possible by inserting photo activated proteins into neurons photo stimulation can produce an olfactory behavior in these larvae , whereas genetically unchanged larvae generally avoid light.

**Animals are not hurt**

Moreover, the researchers could measure the effect electrophysiologically. Thin electrodes can detect the signal of the light-activated neurons. The transmission of the nerve signal can be followed all the way into the brain, thus enabling non-invasive observation of neural networks. Prof. Störtkuhl pointed out that this method has the great advantage of enabling tests to be carried out on living animals without an injury. The research scientists hope to gain an insight into the network and mode of action of the brain. It must moreover be pointed out that the olfactory sense of the genetically modified fly larvae remains normal.

**Same principle applies to other animals**

The researchers now plan to use the same principle to undertake further studies on adult Drosophila, equipping them with photo-activated proteins to cause targeted isolated cerebral neurons to react. These successfully employed methods are now also being used in model systems i.e. mice in other laboratories including a work group at the RUB, to investigate similar issues using mice.

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# Common Cold Virus Efficiently Delivers Corrected Gene To Cystic Fibrosis Cells

July 22, 2009 — Scientists have worked for 20 years to perfect gene therapy for the treatment of cystic fibrosis, which causes the body to produce dehydrated, thicker-than-normal mucus that clogs the lungs and leads to life threatening infections.

Now University of North Carolina at Chapel Hill School of Medicine scientists have found what may be the most efficient way to deliver a corrected gene to lung cells collected from cystic fibrosis patients. They also showed that it may take this high level of efficiency for cystic fibrosis (CF) patients to see any benefit from gene therapy.

Using parainfluenza virus, one of the viruses that causes common colds, the UNC scientists found that delivery of a corrected version of the CFTR gene to 25 percent of cells grown in a tissue culture model that resembles the lining of the human airways was sufficient to restore normal function back to the tissue.

"This is the first demonstration in which we've been able to execute delivery in an efficient manner," said Ray Pickles, Ph.D., associate professor of microbiology and immunology at the UNC Cystic Fibrosis Research and Treatment Center. "When you consider that in past gene therapy studies, the targeting efficiency has been somewhere around 0.1 percent of cells, you can see this is a giant leap forward."

"We discovered that if you take a virus that has evolved to infect the human airways, and you engineer a normal CFTR gene into it, you can use this virus to correct all of the hallmark CF features in the model system that we used," Pickles said. For instance, the experiment improved the cells' ability to hydrate and transport mucus secretions.

Now the researchers must work to ensure the safety of the delivery system. In a pleasant surprise, simply adding the CFTR gene to the virus significantly attenuated it, potentially reducing its ability to cause inflammation. But the scientists may need to alter the virus further.

"We haven't generated a vector that we can go out and give to patients now," Pickles said, "but these studies continue to convince us that a gene replacement therapy for CF patients will some day be available in the future."

In addition to Pickles, UNC co-authors are Liqun Zhang Ph.D, research associate, CF Center; Brian Button Ph.D., assistant professor, CF Center; Sherif E. Gabriel Ph.D., associate professor, pediatrics); Susan Burkett, research analyst, CF Center; Yu Yan, research specialist, CF Center; Yan Li Dang, research specialist, CF Center; Tristan McKay Ph.D., postdoctoral fellow, CF Center; and Richard C. Boucher M.D., Kenan Professor of Medicine, director, CF Center.

Other co-authors are April Mengos of the Mayo Clinic College of Medicine, as well as Mario H. Skiadopoulos, Ph.D., Leatrice N. Vogel and Peter L. Collins Ph.D., all of the National Institute of Allergy and Infectious Diseases, National Institutes of Health.

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