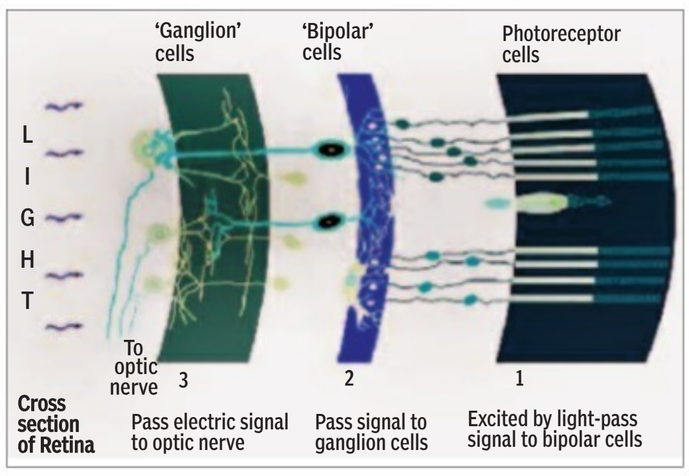
Microchip restores sight

THE MATERIAL OF GLASS SPECTACLES IS GETTING SET TO MOVE INTO THE RETINA, WRITES **S ANANTHANARAYANAN**

Silicon, whose oxide silica is the material of the drinking glass or glass lenses, also gives off electric charges when exposed to light. This is the principle of the light meter and also the solar panel. Implants made of silicon may now take the place of impaired light sensitive cells within human eyes.

Henri Lorach, Georges Goetz, Richard Smith, Xin Lei, Yossi Mandel, Theodore Kamins, Keith Mathieson, Philip Huie, James Harris, Alexander Sher and Daniel Palanker, a multidisciplinary team from Stanford University, University of California, Institut de la vision, Paris, Bar Ilan University in Israel and the University of Strathclyde, Glasgow, report in the journal *Nature Medicine* that one to two-millimetre wide light-sensitive arrays of silicon can be placed inside the retina to provide electrical signals and allow eyes to see with functional clarity. The group has proved the device to work in the rat eye and human clinical trials are planned next year in France.



The retina of the natural eye works as a panel of light-sensitive nerve cells that create electrical signals that pass information to the brain. When light strikes the photoreceptor cell, there is a structural change in molecules in a pigment within the cell, and this affects the movement of charged sodium ions within the cells, creating electrical tension. This is the signal that gets transmitted down to other nerve cells within the retina and then to the brain as brightness in the part of the visual field that the photoreceptor cell represents. There are about 120 million photoreceptor cells in the average human eye, and these are connected to some two million nerve terminals leading to the brain.

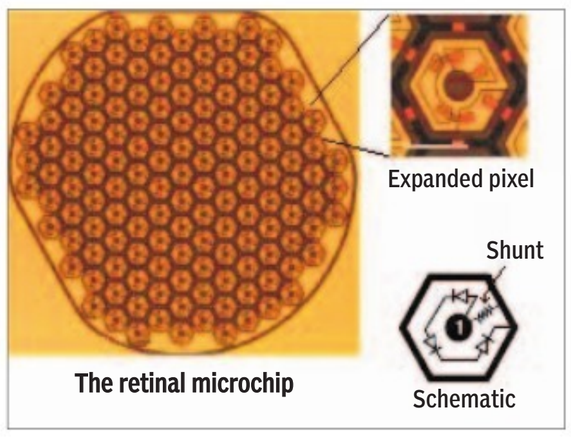
Now, in older people or when there is disease, the photoreceptor cells get damaged and do not initiate an electrical signal when light falls on them. The rest of machinery is intact, but for want of the initial signal sight is not possible and the person is blind in that eye. *Age Related Macular Degeneration* (the macula is the centre of the retina) is a major cause of inability to read or recognise faces in older people, affecting nearly 50 million. There is also a condition of *retinitis pigmentosa*, a hereditary disease where photoreceptor cells decline. The loss of vision progresses from the periphery to the centre and can strike at any age.

No medicines or curative procedures for these conditions are known so far, although the long-term use of saffron (*Crocus sativus*), a spice containing the antioxidant carotenoids crocin and crocetin, has been found to give short-term benefit in early ARMD. The sole recourse has hence been to *retinal prosthetics*. One system is cameras that generate electrical signals that are passed by surgically implanted contacts to the nervous system. The result is not sight but a substitute, and users are able to learn how to use the neural stimuli received to approximate shapes. But bulky implanted electronics and the passing of cables through the lining of the eye with complex surgery are involved.

Another system is of placing the camera and related electronics in a chip that is implanted behind the retina. This device contains tiny photocells to capture light, amplifiers to boost their signal and electrodes to stimulate retinal nerve cells. But the surgery required is even more complex. The cost in both cases is astronomical and the benefit is limited — users can learn just to make out the difference between a doorway and a person or, in some cases, between a fork and a spoon.

Implanting microchips

In contrast, the system reported in the paper in *Nature Medicine* consists of millimetre-scale silicon-based chips to be implanted with relatively less invasive surgery into the retina and, most significantly, does not involve any wiring from the eye to external devices or from devices to the neural network. The chips, in fact, take the place of the degenerate photoreceptor cells and transmission of electrical signals is through the nerve cells in the retina itself, which communicates in turn with the optic nerve.



Each module of the microchip consists of an array of photocell pixels, each one 70 microns wide. Each pixel consists of two or three silicon-based micro-devices that generate a voltage when illuminated, and these are arranged in series. Each pixel then, when activated, generates an electrical potential that is passed down to the nerve cells immediately in contact with the pixel and the whole array stimulates different nerve cells as if by different natural photoreceptor cells.

One detail of the action of the photoreceptor cell is that it rapidly de-excites immediately after it is excited. If this were not the case, each bright point in the visual field would remain bright even after the bright object has moved away and movement could not be made out. The actual nature of the nerve cells in the eye is that their normal condition is to be polarised, or charged with the inflow of sodium ions. The effect of light falling on the cells is that a gateway for the flow of ions gets closed and this changes the charge distribution, which gets passed on from cell to cell as the visual signal. But the ion-gates stay closed only for an instant and the pixel becomes dark if it is not again stimulated by another particle of light.

Flickering of light that is faster than the rate of the relaxing of photoreceptors cannot be made out and this is the way the eyes see motion without breaks on the movie screen, for instance.

The same effect is created in the pixels of the microchip by providing a resistive shunt, or pathway that discharges the pixel a small instant after it has been charged by a particle of light. The pixel would then stop passing a signal to the nerve cells below, unless it is again stimulated by a particle of light, so that it behaves just like a natural photoreceptor cell.

The team of researchers tried out the scheme by implanting one to two-millimtere chips into the retinas of experimental rats, both normally sighted as well as vision impaired. This was a simple surgical procedure compared to implanting other devices that need to be wired and connected. With the insertion of a chip that is one millimetre square, the field covered is of some 250 pixels, which can resolve a reasonable amount of detail.

That the system actually worked was verified first by sandwiching a healthy piece of retina between a photoreceptor chip and an array of electrodes wired into the terminal nerve cells in the patch of retina. Next, for testing in real life, implants were placed in the living retinas of 16 experimental rats. The response to light stimulus was then estimated by connecting electrodes within the eye and the nerve pathway to the brain of the rats and the response checked with stimulus by a pattern of ruled lines and varying the thickness and spacing of the lines.

The results showed that the microchips did create sight and the quality of sight is around "20/250". This a measure that means sight at 20 feet as good as a subject with normal vision would have at 250 feet. (If our eye test gives a reading of "6/6", this means we can see at six metres what a normal person would see at the same six metres. But "6/12" would mean seeing half as well.) In contrast, the elaborate prosthetics so far available are able to provide only "20/1,200". The microchip method is thus about five times more effective. "20/250", incidentally, is like good enough to read the newspaper if the type is large.

The team plans to improve the resolution by reducing pixel size and providing each one with a contact that touches fewer retinal nerve cells. Human trials are then planned in 2016 in collaboration with a French firm, using persons who have lost eyesight through *retinitis pigmentosa* as subjects.

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PLUS POINTS

Search for aliens

The National Aeronautic and Space Administration is bringing together scientists from a range of different fields to try and search for life on other planets. The Nexus for Exoplanet System Science, or NExSS, will bring together earth scientists, who will look to further understand how planets can support life. They will do so by looking at how our earth and the planets around us search for life, and use that to understand how viable newly-discovered planets could be as homes for aliens.

"This interdisciplinary endeavor connects top research teams and provides a synthesised approach in the search for planets with the greatest potential for signs of life," said Jim Green, Nasa's director of planetary science, in a statement. "The hunt for exoplanets is not only a priority for astronomers, it's of keen interest to planetary and climate scientists as well." The team will look to understand exoplanets — those that are around other stars, like earth. It is a new field, beginning when scientists found the first planet that goes around a sun like ours in 1995. Since then, scientists have found more than 1,000 planets, with many more waiting to be confirmed.

NExSS will bring together earth scientists, planetary scientists, heliophysicists who study the sun and astrophysicists who will provide data on the planets themselves.

THE INDEPENDENT

Tinnitus map

A 50-year-old man is helping scientists learn about brain function in people suffering from tinnitus, the maddening condition that affects some 25 million people in the USA. As the patient's skull was opened for the surgical procedure, William Sedley of the University of Newcastle, UK, and his colleagues

implanted 164 electrodes directly into his brain while playing white noise to modulate the intensity of his ear ringing to track neural activity as he suffered from bouts of tinnitus. The results were published in *Current Biology* on 23 April. "What was nice about our experiment was that we could compare the brain activity associated with loud and quiet tinnitus without anything like attention or emotion muddying the waters," Sedley said. "Normally, studies compare brain activity of people with and without tinnitus using non-invasive techniques."

He and his colleagues found that the patient's tinnitus was associated with increased brain activity in the primary auditory cortex, which serves as a sound-processing center, but also in brain areas that are involved with memory, emotion, and attention. "Rather than just a small area of auditory cortex… we found that these correlates of tinnitus were present throughout a huge proportion of the brain areas we sampled," Sedley said. The results represent a high-resolution map of the neural underpinnings of tinnitus and suggest that the condition is not simply the product of alterations within a single hearing pathway. Further investigation may lead the way to improved treatments.

THE SCIENTIST

MOLECULAR CHAPERONES

TAPAN KUMAR MAITRA EPLAINS HOW THESE ASSIST IN THE ASSEMBLY OF SOME PROTEINS

Based on the ability of some denatured proteins to return to their original configuration and to regain biological function as they do, biologists initially assumed that proteins and protein-containing structures self-assembled in cells as well. For ribonuclease, protein synthesis takes place on ribosomes. The polypeptide elongates as successive amino acids are added to one end. The self-assembly model envisions polypeptide chains coiling and folding spontaneously and progressively as polypeptides are synthesised in this way.

By the time the fully elongated polypeptide is released from the ribosome, it is thought to have attained a stable, predictable three-dimensional structure without any input of energy or information beyond the basic polymerisation process. Further, folding is assumed to be unique in the sense that each polypeptide with the same amino acid sequence will fold in an identical, reproducible manner under the same conditions. Thus, the self-assembly model assumes that interactions occurring within and between polypeptides are all that is necessary for the biogenesis of proteins in their functional forms.

However, this model for self-assembly *in vivo* (in the cell) is based entirely on studies with isolated proteins and even under laboratory conditions not all proteins regain their native structure. Based on their work with one such protein *(ribulose bisphosphate carboxylase/oxygenase,* the multimeric enzyme in chloroplasts that catalyses the fixation of $C0_2$ in the process of photosynthesis), John Ellis and colleagues at Warwick University concluded that the self-assembly model may not be adequate for all proteins, at least not in its simplest formulation. In many cases, the interactions that drive protein folding need to be assisted and controlled to reduce the probability of the formation of incorrect structures having no biological activity.

For assembly processes with a low probability of incorrect interactions and nonfunctional structures (as is likely the case of the folding of a protein such as *ribonuclease*, which consists of a single polypeptide chain), such control may not be needed. For more complex processes (such as the assembly of ribulose bisphosphate carboxylase/oxygenase from its 16-component subunits), control is essential to produce a sufficient number of correct structures for cellular needs.

This control of complex assembly processes is exerted by pre-existing proteins called *molecular chaperones*, which facilitate the correct assembly of proteins and protein-containing structures, but are not components of the assembled structures. The molecular chaperones that have been identified to date do not convey information either for polypeptide folding or for the assembly of multiple polypeptides into a single protein. Instead, they function by binding to specific structural features that are exposed only in the early stages of assembly, thereby inhibiting unproductive assembly pathways that would lead to incorrect structures.

Commenting on the term *molecular chaperone,* Ellis and SM Van der Vies observed that "the term chaperone is appropriate for this family of proteins because the role of the human chaperone is to prevent incorrect interactions between people, not to provide steric information for those interactions" (Ellis and Van der Vies, 1991).

John Ellis

The mode of action of molecular chaperones is best described as *assisted self-assembly.* We can therefore distinguish two types of self-assembly: *strict self-assembly,* for which no factors other than the structure of the polypeptide itself are required for proper folding; and *assisted self-assembly,* in which the appropriate molecular chaperone is required to ensure that correct assembly will predominate over incorrect assembly.

The list of known molecular chaperones has grown steadily since Ellis and his colleagues first proposed the term in 1987. The first molecular chaperones studied were those of chloroplasts, mitochondria and bacteria. Within a few years, however, chaperones were identified in other eukaryotic locations. Chaperone proteins are abundant under normal conditions and increase to still higher levels in response to stresses such as increased temperature — a condition called *heat shock* — or an increase in the cellular content of unfolded proteins. Many common chaperone proteins fall into two families called *Hsp60* and *Hsp70.* ("Hsp" stands for *heat-shock protein,* and the numbers refer to the approximate molecular weights of the protein's polypeptide monomers — 60,000 and 70,000, respectively.) The proteins within each Hsp family are evolutionarily related and these are found throughout the biological world. Hsp70 proteins, for example, have been found in bacteria and in cells of a wide variety of eukaryotes, where they are present in several intracellular locations.

One important class of chaperones, *nucleoplasmins,* are nuclear proteins that perform a variety of functions during such nuclear processes as DNA replication, transcription and the processing of RNA, and the transport of molecules into and out of the nucleus.

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A vegetarian dinosaur

A STUDY OF THE 150 MILLION-YEAR-OLD REMAINS FOUND IN CHILE SHOWS THAT THOUGH IT SHARED MANY FEATURES OF ITS CARNIVOROUS T. REX COUSIN, IT GRAZED EXCLUSIVELY ON PLANTS, WRITES **STEVE CONNOR**

Dinosaurs come in all shapes and sizes but there has been nothing quite so unusual as a species found in the Patagonian fossil fields of Chile, scientists have said. A study of the 150 million-year-old remains of a Tyrannosaurus-like dinosaur shows that although it shares many of the features of its more fearsome carnivorous cousin, it grazed exclusively on plants.

Scientists studying the anatomy of *Chilesaurus diegosuarezi* said it was the "platypus" of dinosaurs because of its bizarre combination of specialised features normally seen in quite unrelated animals — similar to the egg-laying, fur-covered features of the duck-billed platypus. Although the species belonged firmly within the two-legged group of dinosaurs called *theropods*, which include such well-known meat-eaters as T. rex, Velociraptor and Carnataurus, it was distinguished from the others by a long neck and proportionally small skull with flat, leaf-shaped teeth for grinding vegetable matter, the researchers said.

The study revealed that Chilesaurus was one of the best known examples of "convergent evolution" within one animal, where a range of characteristics specialised for different functions converge into a single species resulting in a mosaic of physical features. "Chilesaurus can be considered a 'platypus' dinosaur because different parts of the body resemble those of other dinosaur groups due to mosaic convergent evolution. In this process, a region or regions of an organism resemble others of unrelated species because of a similar mode of life and evolutionary pressures," said Martin Ezcurra of Birmingham University.

"Chilesaurus provides a good example of how evolution works in deep time and it is one of the most interesting cases of convergent evolution documented in the history of life," said Dr Ezcurra, who was part of the Chilean-led team whose study is reported in the journal *Nature.*

Chilesaurus diegosuarezi is named after a seven-year-old boy, Diego Suarez, who was the first person to discover its fossil remains while searching for decorative stones with his family among rocks deposited at the end of the Jurassic Period in the Toqui Formation in Ayzen, south of Chilean Patagonia. He was visiting the area with his parents, who are professional geologists studying this rock formation in the Andes mountain range to better understand how they were formed. Since his initial find, more than a dozen specimens of *Chilesaurus* have been unearthed in the area, including four complete skeletons, making it one of the most common dinosaurs of South America.

Anatomical comparisons have shown that the bipedal *Chilesaurus* had relatively short but strong forelimbs similar to T.rex and other carnivorous therapods.

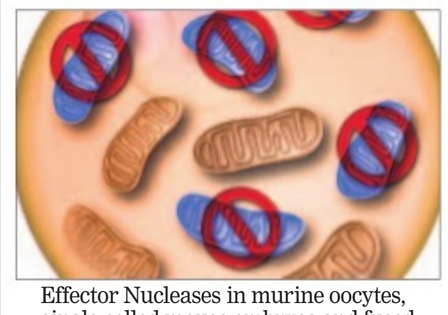
However, its hands had two blunt fingers, unlike the sharp, dagger-like claws of meat-eaters such as Velociraptor. "Chilesaurus is the first complete dinosaur from the Jurassic Period found in Chile and represents one of the most complete and anatomically correct documented theropod dinosaurs from the southern hemisphere," said Fernando Novas of the Bernadino Rivadavia Natural Sciences Museum in Buenos Aires, Argentina.

"Although plant-eating theropods have been recorded in North America and Asia, this is the first time a theropod with this characteristic has been found in a southern landmass," said Dr Novas, the lead author of the study.

THE INDEPENDENT

Erasing mutations

Mutations in mitochondrial DNA (mtDNA) can be specifically targeted and removed by Transcription Activator-Like



Effector Nucleases in murine oocytes, single-celled mouse embryos and fused human-mouse hybrid cells, providing proof of principle for a method that could one day be used to treat certain hereditary mitochondrial disorders in people, according to a study published on 23 April in *Cell.*

"It's an extremely important step," said Valerio Carelli of the University of Bologna, Italy. "The results are very relevant and very convincing."

THE SCIENTIST