Retina repair in sight

Solar cell material may help the visually impaired to see, says s ananthanarayanan

SOLAR cells create electricity when sunlight falls on them. The cells of the retina do the same thing, sending pulses of electricity to the optic nerve when exposed to light. While there has been no way to repair damaged retinas, it is tempting to think of using solar cell material to take their place.

The trouble is that solar cells have traditionally used metallic components, like silicon or germanium crystals, materials that cannot be integrated with living tissue in animals. The discovery of organic materials that could work as solar cells raised hopes that synthetic materials, which are known to interface with biological tissue, may find a place in the eye.

Diego Ghezzi, Maria Rosa Antognazza, Rita Maccarone, Sebastiano Bellani, Erica Lanzarini, Nicola Martino, Maurizio Mete, Grazia Pertile, Silvia Bisti, Guglielmo Lanzani, scientists in Geneva, Milan, and L'Aquila and Negrar, Italy, report in the journal *Nature Photonics* that a popular synthetic material is shown to efficiently stimulate nerve cells and restore light sensitivity in a damaged retina. "Interfacing organic electronics with biological substrates offers new possibilities for biotechnology…" say the authors of the paper.

Photo cells and solar cells work, thanks to the

Edmund Becquerel.

forms a balanced lattice because it has four outer shell electrons. Now, if the lattice is "doped" with, or impurities added, other atoms that have either three or five outer electrons, like phosphorus or boron, then, at each of these atoms, the lattice would have

Alan J Heeger, Alan MacDiarmid and Hideki Shirakawa.

photovoltaic effect, a property of some metals, discovered in 1839 by Edmund Becquerel, then a 19-year-old French scientist. In metals that form a balanced crystal lattice, like silicon, where the four outer shell electrons of each atom "hold hands" with a similar electron of a neighbouring atom, the forces that bind the electrons to the atoms get diluted and the outer electrons can be nudged to escape the parent atom and "float", to conduct electricity. In metals like silicon, the "nudge" can be gentle and photons of light can provide the necessary energy. But this effect is not of use by itself, as the atom that has yielded an electron would be left with a net positive charge, which would rapidly bring the fugitive electron back.

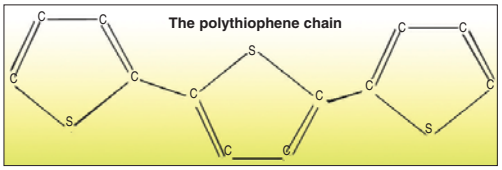
The way the electrons that are freed by a photon are made to do work, as an electric current before they go back to where they belong, is to trap the free electrons behind a "one-way" gate so that they need to flow through an electric circuit to return. The one-way gate is created by using silicon in two modified forms of lattice, in conjunction. The silicon atom one electron "short" or "too many". Such "extra" electrons, or the lack of one, which are called *holes*, equally help carry electricity and materials that have been treated in this way are called *semiconductors*. And when there is a junction of the two kinds of semiconductors, then the electron carriers on one side of the junction can pass into the next one, but the "holes" on the other side cannot move to the "extra" electron side.

The junction is thus *one way*. In a stack of these two kinds of semiconductors, electric charge builds up on the opposite sides of the "gate" and this can drive a current through a device or charge a battery. We can see that it is a *donor-acceptor* mechanism that is in action.

Organic photo-material

Just like silicon and germanium have four outer shell electrons that give them special properties, the simpler element, carbon, also has this for-electron structure. And, thanks to its lower mass, carbon is able to easily form a variety of compounds with oxygen, hydrogen and other elements like sulphur, chlorine and nitrogen. These compounds are stable and engage in reactions at normal temperature and pressures and hence all life, vegetation and animal, is carbon-based – which gives this class of compounds the name *organic*. As organic compounds arise from chemical combinations, where the outer electrons of atoms engage with other atoms, the electrons are not usually free to conduct electricity and organic materials have not been of great use in this area, except as insulators.

An exception is the class of conducting polymers that are organic molecules with a long, repeating structure, with bonds that allow electrons to get free. Important work on these compounds was done by Alan J Heeger, Alan MacDiarmid and Hideki Shirakawa and they received the Nobel Prize for Chemistry for 2000 for their work. In this work, they developed a class of compounds, the *polythiophenes (PTH)*, which occur as chains of units of five-sided



rings, each with one sulphur and four carbon atoms at the corners, with the bonds between atoms being the "sharing" of outer shell electrons. The carbon atoms participate in the ring by sharing one electron with one neighbour, two electrons with the next and the last electron with some chemical group outside the ring. This combination of single and double bonds allows an electron to become free to conduct and also allows "doping" where there can be an "extra" or a "one short" electron, although it is the "extra" that is common.

This class of compound has a marked response to exposure to light and has given rise to the field of organic or *polymer solar cells*. These consist of an optically active layer sandwiched between an electron or hole blocker, mounted on a conducting glass surface and a metallic electrode. The device is much lighter and cheaper than silicon-based devices, apart from being flexible, so that it can be rolled into sheets. The material can also be customised, during preparation, to suit the kind of light source it is to be used with. But the disadvantage is that it is only one-third as efficient as silicon-based devices. But the promise of cheap and largescale deployment has led to a huge research effort and the improvements in efficiency that have been achieved are perhaps more than what has been reported.

One of the most successful materials for this kind of application is the blend of a PTH, an electron donor, and a Fullerene molecule, which has a shape like a geodesic dome or a football, which acts as an electron acceptor – thereby enabling the proven *donor-acceptor* mechanism. Apart from a high figure of efficiency in its use in solar cells, this blend has also proved successful in stimulating nerve cells cultured on a substrate, or platform, of the blend. The authors of the paper point out that the manner of working, when in contact with biological material, may be different from the electron exchange mechanism in the usual solar cell design. With biological material, it may be a case of charges on one side of the interface inducing corresponding effects on the other side, rather than a physical current.

The Italian team carried out detailed studies with the electron donor, or PTH part of the blend, alone and the retinal nerve cells extracted from albino rats. The light sensitive layer of the retina was degenerated and the depleted cells were placed on specially treated glass coated with PTH. Trials then showed that levels of low illumination, which had no effect on retinal cells placed on just the prepared glass, had a marked effect when the cells were place on glass coated with PTH. As a sequel, the team tried out the PTH layer not with nerve cells but with the retina itself of albino rats, where the photoreceptors of the receptors had been damaged. The exciting discovery was that the level of response was as good as with a normal retina – which holds out the possibility of using light-sensitive polymers for sight restoration of the visually impaired!

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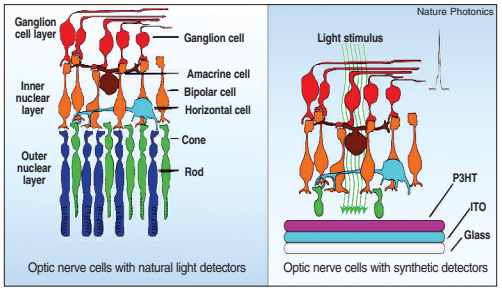


This is deep

steve connor **reports on bacteria discovered in Mariana Trench, a gigantic chasm in the seabed that is big enough to swallow Mount Everest entirely**

SCIENTISTS have found a thriving community of microbes living at the deepest known point on the surface of earth — a massive underwater canyon in the Pacific Ocean 11 km below sea level.

The bacteria were recovered from muddy sediments at a point underneath the central west Pacific called Challenger Deep in the huge Mariana Trench, a gigantic chasm in the seabed that is big enough and deep enough to swallow Mount Everest whole.

The central part of the autonomous instrument that was deployed to measure the oxygen dynamics of the seabed in the Mariana Trench at a depth of 11 km. Data documented intensified microbial life at the bottom of the trench as compared to conditions at the surrounding abyssal plains at a depth of six kilometres.

Marine biologists said they were astonished to find such an abundance of microbial life-forms living off the dead and decaying matter that sinks to the deepest parts of the ocean where pressures are more than 1,000 times greater than at sea level.

"These microbes may in fact be the ones that are the closest to the centre of the earth, the deepest living organisms that we have seen. They are probably the deepest observed community of microbes below sea level," said Professor Ronnie Glud of the University of Southern Denmark. "We expected to see microbes there but we didn't expect them to flourish and to be so efficient. What is really surprising is that we have seen bacteria that operate so efficiently at these depths."

A deep-sea submersible robot that can analyse life-forms *in situ* discovered the microbial community in sediment samples taken in 2010 from the Mariana Trench. The sediment has built up over tens of thousands of years and is probably several hundreds of metres deep, he said. "If we retrieve samples from the seabed to investigate them in the laboratory, many of the micro-organisms that have adapted to life at these extreme conditions will die, due to the changes in temperature and pressure. Therefore, we have developed instruments that can autonomously perform pre-programmed measuring routines directly on the seabed at the extreme pressure of the Mariana Trench... We find a world dominated by microbes that are adapted to function effectively at conditions highly inhospitable to most higher organisms," he said.

the independent

Organelles and human diseases

Most of the ailments associated with mitochondrial defects are characteristic of either muscle or nerve tissue, which is not surprising, writes tapan kumar maitra

ALTHOUGH we may not often acknowledge it — indeed, we may not even be aware of it — many human diseases are actually caused by molecular malfunctions within specific organelles. The list of organelle-linked diseases is lengthy, including such diverse mitochondrial disorders as myopathies (diseases or disorders of muscle cells), Leigh syndrome (a devastating neurodegenerative disorder), and fatal infantile respiratory defects. Also included are peroxisomal disorders such as Zellweger syndrome and neonatal adrenoleuko-dystrophy, as well as more than 40 lysosomal storage diseases, each marked by the harmful accumulation of specific substances.

We will consider several of these diseases here, though only in an introductory manner. In the process, we will anticipate discussions of the functions localised to several organelles, including mitochondria as well as peroxisomes and lysosomes.

Most of the diseases associated with mitochondrial defects are characteristic of either muscle or nerve tissue, which is not surprising given the high rates of Adenosine triphosphate (ATP) consumption by these tissues and the essential role of the mitochondrion in ATP synthesis. The list includes at least 35 myopathies as well as a variety of disorders that affect nerve function. Depending on the specific defect, these disorders range greatly in severity. Some lead to infant death, others result in blindness, deafness, seizures, or stroke-like episodes. Milder forms, on the other hand, are characterised by muscular weakness, intolerance of exercise, muscle deterioration and, in some cases, by infertility due to non-motile sperm.

These are all genetic disorders and to understand them we need to know that mitochondria have a limited amount of their own DNA. The mitochondrion encodes some, though by no means all, of its own proteins. Human mitochondrial DNA (mtDNA) contains 37 genes, of which 22 specify transfer RNAs (tRNAs), two specify ribosomal RNAs (rRNAs) and the remaining 13 genes encode polypeptides, all of which are components of the respiratory complexes that carry out oxygen-dependent ATP synthesis.

Although the respiratory complexes also contain about 70 nuclear-encoded polypeptides, most of the known mitochondrial myopathies are due to defects in mitochondrial rather than in nuclear genes, involving either the deletion or mutation of specific mitochondrial genes. Most of these defects occur in the genes that encode mitochondrial tRNAs, which are required for the synthesis of all 13 mitochondrially encoded polypeptides. Examples of these diseases include mitochondrial encephalomyopathy and hypertrophic cardiomyopathy, which affect the brain and heart, respectively, and are due to defects in the tRNAs for the amino acids leucine and isoleucine, respectively.

Mitochondrial disorders follow what is called maternal inheritance, which means they come exclusively from the mother. Since all human mitochondria are derived from the mitochondria that were present in the egg at the time of fertilisation, the sperm cell provides its half of the nuclear genome but makes little or no mitochondrial contribution. A further distinction between nuclear and mitochondrial genes is that a typical human cell contains hundreds of mitochondria, each with two to 10 copies of mtDNA, so the cell contains thousands of copies of mtDNA. As a result, mtDNAs can be quite heterogeneous within specific tissues and mitochondrial disorders are likely to arise only when most of the mitochondria within a given tissue contain a particular mutant gene.

Most of the human diseases associated with peroxisomes are due to the absence of a single peroxisomal protein. Considering the variety of cellular functions that are localised to this organelle, it is not surprising that a large number of disorders are known in which specific peroxisomal proteins are either defective or absent. Unlike mitochondria, peroxisomes contain no DNA; thus, all of these defects are due to mutations in nuclear genes.

Three well-studied peroxisomal disorders are Zellweger's syndrome (ZS), Neonatal adrenoleukodystrophy (Nald) and Infantile refsum disease (Ird). ZS is characterised by a variety of severe neurological, visual and liver disorders that lead to death during early childhood. Nald is a sex-linked (male-only) disease that is typically less severe than ZS but eventually leads to neurological impairment and death. Boys with Nald usually begin to display symptoms of adrenal failure and neurological debilitation during early childhood. The symptoms of Ird are similar to, but less severe than, those of ZS and Nald.

Although these diseases were discovered independently and not initially considered to be related, we now know that each is caused by mutations in any of 11 different human genes. The most severe mutations cause ZS, moderately severe mutations cause Nald, and the least severe mutations cause Ird.

In some forms of Nald, the defective gene product is a membrane protein involved in the transport of very long-chain fatty acids into the peroxisome, where such acids are broken down to shorter-chain lengths that can be handled by the mitochondrion. When this transport mechanism is impaired or nonfunctional, the very long-chain fatty acids accumulate in cells and tissues. That accumulation is particularly devastating in the brain, where they destroy the myelin sheaths that provide essential insulation for nerve cells, thereby profoundly impairing transmission of neural signals.

In ZS, the missing or defective gene product can be any of several proteins that are essential for targeting peroxisomal enzymes for uptake by the organelle. Peroxisomal proteins are encoded by nuclear genes and then imported into the peroxisome. Individuals with ZS can typically synthesise all of the requisite enzymes but they have a deficiency in any of several membrane proteins involved in the transport of these enzymes into the organelle. As a result, the proteins remain in the cytosol, where they cannot perform their intended functions.

Peroxisomes can be detected in the cells of such individuals, but the organelles are empty "ghosts" — membrane-bounded structures without the normal complement of enzymes. Not surprisingly, afflicted individuals develop a variety of neurological, visual and liver disorders that lead inevitably to death during early childhood.

Another organelle subject to a variety of genetic defects is the lysosome, which plays an essential role in the digestion of food molecules and in the recycling of cellular components that are no longer needed. Over 40 heritable lysosomal storage diseases are known, each characterised by the harmful accumulation of a specific substance or class of substances, most commonly polysaccharides or lipids, that would normally be catabolised by the hydrolytic enzymes present within the lysosome. In some cases, the defective protein is either a key enzyme in the degradation of the substance or a protein involved in the transport of the degradation products out of the lysosome.

In other cases, the requisite enzymes are synthesised in normal amounts but are secreted into the extracellular medium rather than being targeted to the lysosomes.

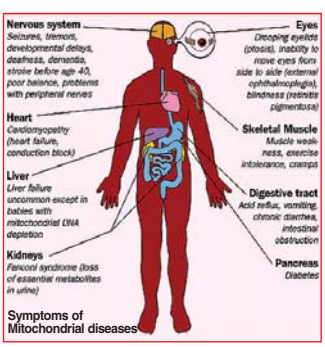
An example of this latter type of disorder is I-cell disease, which is due to a defect in an enzyme called N-acetylglucos-amine phosphotransferase. This enzyme is required for the correct processing of the portion of the protein that targets, or signals, lysosomal enzymes for import into the organelle. In the absence of the necessary signal, the hydrolytic enzymes are not transported into the lysosomes. Thus, the lysosomes become engorged with undegraded polysaccharides, lipids and other material. This causes irreversible damage to the cells and tissues.

A well-known example is Tay-Sachs disease, which is quite rare in the general population but has a higher incidence among Ashkanazi Jews of eastern European ancestry. After about six months, children who are homozygous for this disease show rapid mental and motor deterioration as well as skeletal, cardiac and respiratory dysfunction, followed by dementia, paralysis, blindness and death, usually within three years. The disease results from the accumulation in nervous tissue of a particular glycolipid called ganglioside G_{M2}.

The missing or defective lysosomal enzyme is β-N-acetylhexosaminidase A, which cleaves the terminal N-acetylgalatosamine from the "glyco" (carbohydrate) portion of the ganglioside. G_{M2} is a prominent component of the membranes in brain cells. Not surprisingly, lysosomes from children afflicted with Tay-Sachs disease are filled with membrane fragments containing undigested gangliosides.

All of the known lysosomal storage diseases can be diagnosed prenatally. Even more significant are the prospects for enzyme replacement therapy and gene therapy. Enzyme replacement therapy has been shown to be effective with a particular lysosomal disorder called Gaucher's disease, characterised by the absence or deficiency of a specific hydrolase called gluco-cerebrosidase. In the absence of this enzyme, lipids called gluco-cerebrosides accumulate in the lysosomes of macrophages, which are the white blood cells that engulf and digest foreign material or invasive micro-organisms as well as cellular debris and whole damaged cells.

Glucocerebroside accumulation typically leads to liver and spleen enlargement, anaemia, and mental retardation. Treatment depends on the ability to purify gluco-cerebrosidase from human placental material, treat it so that it will be recognised by receptors on the surface of macrophages and taken up by these cells specifically, and infuse it into the bloodstream. Macrophages that are treated in this way are able to degrade glucocerebrosides as needed, thereby effectively treating what would otherwise be a fatal disease. Gene therapy is a somewhat more futuristic prospect for the treatment of lysosomal storage diseases, as well as other heritable disorders. This approach involves the insertion of the genes for the missing enzymes into the appropriate cells, thereby effectively curing the disease rather than simply treating it.



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