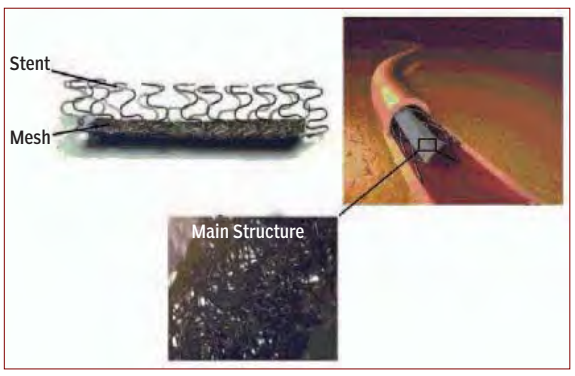
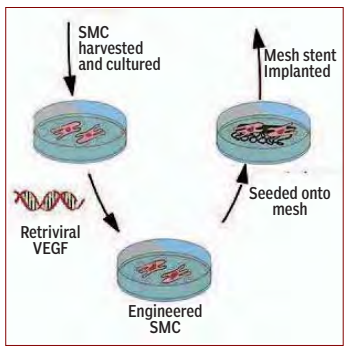
Fixing the heart without surgery

MICRO-BYPASS, WHICH THE BODY BUILDS FOR ITSELF, WOULD OPEN MANY DOORS IN CARDIAC CARE, SAYS **S ANANTHANARAYANAN**



Heart disease in the form of blocked coronary arteries and muscles starved of blood supply, which means oxygen and glucose, is a leading cause of disability and death. Surgical intervention to create alternate paths around the blocks is often not possible and, in any case, is fraught with risk. An alternative possibility, which has been worked on in the last two decades is to flood the place that has the blockage with gene and protein material, which promotes the growth of new blood vessels so that a path around the block develops without the need for a surgical cut-and-splice operation. But methods to actually deliver the right quantities of carriers of these therapeutic agents where they are needed and to ensure that they stay there have been elusive.

Arun HS Kumar, Kenneth Martin, Brendan Doyle, Chien-Ling Huang, Gopalakrishnan M Pillai, Mohammed T Ali, Kimberly A Skelding, Shaohua Wang, Birgitta M Gleeson, Saleem Jahangeer, Erik L Ritman, Stephen J Russell and Noel M Caplice of University College Cork, in Cork, Ireland, and Mayo Institute in Rochester, USA, report in the journal *Biomaterials* that they have tried out a way of placing cells that contain the blood vessel growth promoting gene in a mesh of metallic fibres. The mesh was moved down the artery to the site of blockage and pressed against the vessel wall using light metal springs, so that the payload in the mesh could promote the growth of new blood vessels at the right place and in a sustained way.

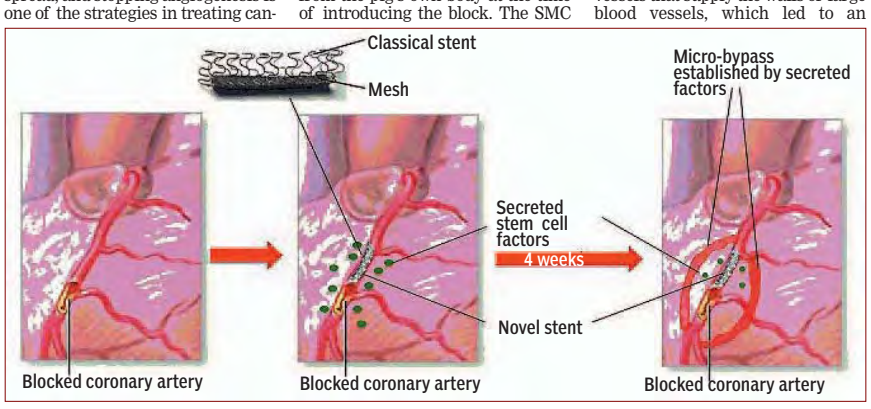


Angiogenesis is the name given to the creation of new blood vessels from pre-existing ones. Specific agents that bring this about, from scratch, are needed during the development of the embryo for the formation of the circulation system. These agents then continue their work to maintain the system of veins and arteries because less hardy blood vessels, like capillaries, suffer damage all the time. Body cells are able to recognise damage to blood vessels when they sense that the supply of oxygen that comes through these vessels has started to drop. When oxygen supply runs low, cells are programmed to generate a family of proteins known as *Vascular Endothelial Growth Factors*, which promote the growth of the *endothelium*, or inner layer of blood vessels.

The endothelial cells line the entire circulatory system, from the heart to the capillaries, and VEGF prompt them to break free and form sprouts that can grow into new blood vessels. This action can progress at the rate of several millimetres a day and is responsible for the growth of vessels to connect gaps in the network of capillaries.

The possibility of swamping the site of an artery block with VEGF to promote the growth of blood vessels, which could form alternate paths in cardiac arteries, was tantalising, say the authors of the paper in *Biomaterials*. While physically taxing and hazardous bypass surgery was so far the only option when there was near total blockage, the need now was to find a way to deliver, and retain at the site, genetic or cellular material that could generate VEGF in good quantity. Experiments carried out on animals had not been significantly successful and rapid angiogenesis often led to the formation of tumours.

Angiogenesis, in fact, is one of the instruments used by cancers to spread, and stopping angiogenesis is one of the strategies in treating cancers. But in trying to promote blood vessel growth for cardiac care, the problem was to control and continue the delivery of therapeutic material to the site.



The Ireland and Rochester group has devised a tiny cartridge resembling a needle which could be introduced into blood vessels with "keyhole" surgery. The device is a mesh of metal fibre, as shown in the picture, and can be fixed against the blood vessel side at the place where required, with the help of thin springs that press against the opposite side of the vessel but do not obstruct blood flow. This is an arrangement, called a *stent*, which is already in use to widen constricted blood vessels. While the mesh could thus be fixed in position, the mesh was first prepared with its payload of cells that would generate VEGF.

Generating VEGF

The trial reported in the journal is of a device used in a pig heart, in an artery in which a block was introduced. The payload in the mesh consisted of Soft Muscle Cells taken from the pig's own body at the time of introducing the block. The SMC was genetically engineered by introducing the genetic code into their DNA with the help of a reverse-acting form of virus, to generate VEGF protein. The cells were cultured externally for four weeks and then introduced into the mesh, which was placed, with the help of a catheter introduced through a major artery, within the cardiac blood vessel of the pig at the site of the block.

CT scanning, X-Ray, microparticle assays, introduction of investigative catheters and tests of heart function were carried out just before the mesh was placed, which was four weeks after the block was introduced, and again four weeks after the mesh, when the pig hearts were also dissected. Twenty-eight Yorkshire pigs were used for the trial and they were divided into two groups, one which received the procedure and the other which did not, as a control group.

Investigators were not aware of which group any pig they were dealing with came from. The results are reported to show a marked increase in the network of the small blood vessels that supply the walls of large blood vessels, which led to an increase in the levels of VEGF protein and the formation of colonies of cells that line blood vessels. These results suggest that the procedure clearly had the potential to increase the generation of new blood vessels. The procedure also markedly increased blood flow in the region and this was reflected in a more efficient pumping action of the heart.

"Our data indicate robust, clinically relevant angiogenesis can be achieved in a pig heart with an artery block, which models the same condition in humans," say the authors of the paper. Further work in this procedure could lead to its use to deliver different curative substances — VEGF is not the only one — to create alternative blood paths in cases of blocked blood vessels, and without recourse to major surgery, they say.

THE WRITER CAN BE CONTACTED AT
simplescience@gmail.com

PLUS POINTS

'Flurry of flares'

It seems like the sun finished August with a bit of a bang. The latest footage from the National Aeronautical and Space Administration's Solar Dynamics Observatory showed a region of the

The sun produced a flurry of flares last week, unleashing over half a dozen solar flares in a day.

sun unleashing over half a dozen solar flares between 25 and 26 August. It emitted a mid-level solar flare that erupted on the left side of the sun followed by several more. While solar flares are powerful bursts of radiation, harmful radiation cannot pass through the earth's atmosphere and affect people on the ground. Two of the flares were classified as M5, which is 10 times less powerful than the most intense of flares, X-class ones.

The other flares were smaller than the M5s. Nasa captured the event in a wavelength of extreme ultraviolet light that is perfect for observing flares. While these M5 and lesser flares were only moderate, some flares, when intense enough, can disturb the atmosphere's layer where GPS and communication signals travel.

Fortunately, there were few reports of people's satnavs going haywire during the August bank holiday.

KIRAN MOODLEY/THE INDEPENDENT

'No panacea'

Research is "not a panacea" for development in low-income countries despite making "important and significant contributions to socio-economic development", according to an impact review of public research by the UK Department for International Development. Evidence

does not back commonly held assumptions about how research leads to change, for example by directly benefiting economic growth and the quality of higher education, the report says.

The lack of impact may be due to a poor interface between science and policy, and weak technology transfer environments need to convert knowledge into useful products, it says. But it does add that funding research may lead to improvement of the skill base necessary for development and, to an extent, design of pro-poor technologies. The authors of the report were unavailable for comment.

The findings challenge the prevalent view among decision-makers in donor countries that simply supplying the resources to create knowledge will solve most problems, says Ajoy Datta, a research fellow in the Overseas Development Institute's Research and Policy in Development unit. "What they don't see are the complicated interactions between multiple actors which determine the outcomes of scientific activity," he says. "Research and researchers have a certain role in this mix but it is quite small."

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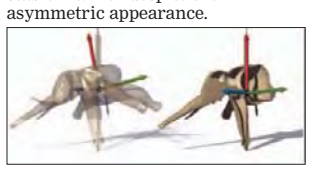
Optimising inertia

Tops and yo-yos have long fascinated cultures around the world with their unexpected, graceful motions that seemingly elude gravity. So here's an algorithm that generates designs for spinning objects by optimising rotational dynamics properties. As input, the user provides a solid 3D model and a desired axis of rotation and the approach then modifies the mass distribution so that the principal directions of the moment of inertia align with target rotation frame. The method is well suited for a variety of 3D printed models, ranging from characters to abstract shapes and this is how tops and yo-yos spin surprisingly in a stable manner despite their asymmetric appearance.



IN CLOSE PROXIMITY

TAPAN KUMAR MAITRA EXPLAINS THE SEVERAL KINDS OF BONDS AND INTERACTIONS THAT ARE IMPORTANT IN PROTEIN FOLDING AND STABILITY

The initial folding of a polypeptide into its proper shape, or conformation, depends on several different kinds of bonds and interactions, as does the subsequent maintenance and stability of that conformation. The most important of these bonds and interactions include the covalent disulfide bond and several non-covalent interactions.

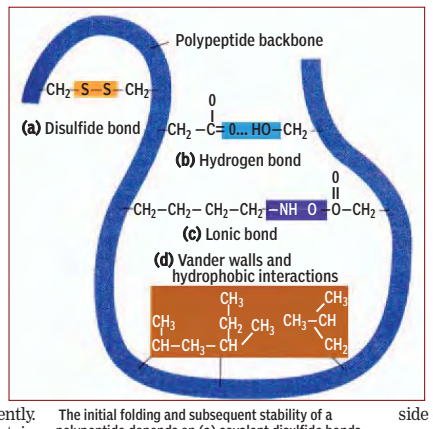
The most common covalent bond that contributes to the stabilisation of protein conformation is the *disulfide bond* that forms when the sulfhydryl groups of two cysteine residues react oxidatively. Once formed, a disulfide bond confers considerable stability because of its covalent nature. It can, in fact, be broken only by reducing it again and regenerating the two sulfhydryl groups. In many cases, the cysteine residues involved in a particular disulfide bond are part of the same polypeptide and are usually quite distant from each other along the polypeptide but are juxtaposed by the folding process.

Such intramolecular disulfide bonds stabilise the conformation of the polypeptide, as is the case for ribonuclease, the monomeric protein we encountered. In the case of multimeric proteins, a disulfide bond may form between cysteine residues located in two different polypeptides. Such intermolecular disulfide bonds link the two polypeptides to one another covalently. The hormone insulin is a dimeric protein that has its two sub-units linked in this manner.

Insulin consists of two polypeptides, called the A and B sub-units, which are covalently linked by two disulfide bonds. As important as covalent disulfide bonds are in maintaining protein structure, noncovalent bonds and interactions are even more important, mainly because they are so diverse and numerous. These include hydrogen bonds, ionic bonds, van der Waals interactions and hydrophobic interactions.

In the case of water molecules, a hydrogen bond forms between a covalently bonded hydrogen atom on one water molecule and a pair of nonbonding electrons of the oxygen atom on another molecule. In the case of a polypeptide, hydrogen bonding is particularly important in stabilising helical and sheet structures that are very prominent parts of many proteins. In addition, the R groups of many amino acids have functional groups that are either good hydrogen bond donors or good acceptors, allowing hydrogen bonds to form between amino acid residues that may be distant from one another along the amino acid sequence but brought in close proximity by the folding of the polypeptide.

Examples of good donors include the hydroxy groups of several amino acids and the amino groups of others. The carbonyl and sulfhydryl groups of several other amino acids are examples of good acceptors. An individual hydrogen bond is quite weak, but hydrogen bonds are very numerous in biological macromolecules such as proteins and DNA and become, in the aggregate, a force to be reckoned with.



The initial folding and subsequent stability of a polypeptide depends on (a) covalent disulfide bonds and several kinds of noncovalent bonds and interactions, including (b) hydrogen bonds, (c) ionic bonds, (d) van der Waals interactions, and hydrophobic interactions.

The role of ionic bonds (or electrostatic interactions) in protein structure is easy to understand. Because the R groups of some amino acids are positively charged and the R groups of others are negatively charged, polypeptide folding is dictated in part by the tendency of charged groups to repel groups with the same charge and to attract groups with the opposite charge. Several features of ionic bonds are particularly significant. The strength of such interactions allows them to exert an attractive force over greater distances than some of the other noncovalent interactions. Moreover, the attractive force is nondirectional, so that ionic bonds are not limited to discrete angles, as is the case with covalent bonds. Because ionic bonds depend on both groups remaining charged, they will be disrupted if the pH value becomes so high or so low that either of the groups loses its charge. This loss of ionic bonds accounts in part for the denaturation that most proteins undergo at high or low pH.

Interactions based on charge are not limited to ions that carry a discrete charge. Even molecules with nonpolar covalent bonds may have transient positively and negatively charged regions. Electrons are in constant motion and are not necessarily always symmetrically distributed about the molecule. At any given instant, the density of electrons on one side of an atom may be greater than on the other side, even though the atom shares the electron equally with another atom. These momentary asymmetries are called dipoles and when two molecules that have such transient dipoles are very close to each other and are oriented appropriately with respect to each other, they are attracted to each other, though for only as long as the asymmetric electron distribution persists in both molecules. This transient attraction of two nonpolar molecules is called a van der Waals interaction, or van der Waals force. A single such interaction is not only very transient; it is also very weak and is only effective when the two molecules are very close together. But these are, nonetheless, important in the structure of proteins and other biological macromolecules and also in the binding together of two molecules with complementary surfaces.

The fourth type of noncovalent interaction that plays a role in maintaining protein conformation is usually called a hydrophobic interaction, but it is not really a bond or interaction at all. Rather, it is the tendency of hydrophobic molecules or parts of molecules to be excluded from interactions with water molecules. The side chains of the 20 different amino acids vary greatly in their affinity for water. Some of them have R groups that are hydrophilic and capable of forming hydrogen bonds not just with each other but also with the water molecules of the medium. Not surprisingly, such groups tend to be located near the surface of a folded polypeptide, where they can interact maximally with the surrounding water molecules.

Overall, then, the stability of the folded structure of a polypeptide depends on an interplay of covalent disulfide bonds and four noncovalent factors: hydrogen bonds between side groups that are good donors and good acceptors; ionic bonds between charged amino acids; R groups, transient van der Waals interactions between nonpolar molecules with temporary electron asymmetries; and hydrophobic interactions that drive nonpolar groups to the interior of the molecule.

THE WRITER IS ASSOCIATE PROFESSOR, HEAD, DEPARTMENT OF BOTANY, ANANDA MOHAN COLLEGE, KOLKATA, AND ALSO FELLOW, BOTANICAL SOCIETY OF BENGAL, AND CAN BE CONTACTED AT
tapanmaitra59@yahoo.co.in

The 'spotless' mouse

CHARLIE COOPER REPORTS ON HOW SCIENTISTS HAVE SUCCESSFULLY ERASED BAD MEMORIES IN RODENTS

Scientists have successfully manipulated the brains of mice to remember unhappy experiences in a positive way, in a study that reveals the extent to which our emotional recollections of life may be "reversible". In a novel experiment, they were able to identify which parts of the brain were involved in forming emotional responses to remembered places or events. By manipulating the brain cells of the mice, they were able to eradicate a fearful memory associated with a particular part of their enclosure, and were also able to associate fear with an area the mouse had previously linked with pleasant experiences.

The emotions that we attach to events in our past are one of the key pillars of our sense of self, but can also be the root of serious psychological problems such as Post-Traumatic Stress Disorder. Scientists from Massachusetts Institute of Technology and Japan's Riken Institute, who carried out the study, said the insights gained into memory formation in the brain could one day help develop drugs to treat people suffering from painful memories. Our memories are believed to be formed by two separate parts of the brain.

Information about a memory's context, such as where and how something happened, are stored in cells of the hippocampus. Emotions linked to that memory are stored in the amygdala. Usually, the learning process allows links between these two areas to form. In the study, one group of mice were exposed to a mild electric shock in a new part of their enclosure, while another group was given a pleasant experience — in this case, "socialising with a female mouse".

The scientists were able to identify the neurons that were active during the forming of each memory. These same neurons were then manipulated using a technique called optogenetics, which uses light-sensitive organisms to control cell activity. Mice which had experienced the electric shock would initially avoid an area of their cage where the lighting was set to "activate" the negative memory, while mice which had been conditioned with the pleasant memory spent more time in the area where that memory was activated. Two days later, the scientists set out to reverse the mice's emotional response by exposing them to negative and positive experiences again, but this time while activating areas of the brain associated with the opposite emotional response.

This time, mice that had avoided the negative area of their cage spent more time there and those that had sought out the positive area of theirs now avoided it. In essence, the mice's memory of what was pleasant and what was unpleasant had been reversed. The study, which has been published in the journal *Nature*, is the closest scientists have yet come to the kind of memory manipulation explored in films like *Eternal Sunshine of the Spotless Mind* and *Inception*. "In the future, one may be able to develop methods that help people to remember positive memories more strongly than negative ones," said Susumu Tonegawa, director of the Riken-MIT Centre for Neural Circuit Genetics and the senior author of the paper.

However, Dr Anders Sandberg, neuroscientist and ethicist at the University of Oxford's Future of Humanity Institute, said that in the future any similar techniques would have to be used with caution.

THE INDEPENDENT