

ISSUE 13 JANUARY 2011

Big Picture

BRINGING CUTTING-EDGE SCIENCE INTO THE CLASSROOM

THE CELL

Insider knowledge

Revealing the secrets of your cells

- What are cells for?
- How do cells divide, develop and communicate?
- What are stem cells and why are they important?
- What happens when cells die?

A resource for teachers and learners

FREE

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Big Picture

Big Picture is a free resource for teachers, school and college students, and learners of any age. Published twice a year, each issue comes as a printed magazine with accompanying online articles and other content. Here's how to get the most from your issue.

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How to use *Big Picture* magazine

Each issue of *Big Picture* focuses on a topic that is current, relevant to the biology curriculum, rooted in science, and that has debate-provoking aspects. The issues are divided into double-page spreads, each dealing with a different aspect of the topic.

The spreads are a jigsaw of articles, images, diagrams and 'Fast Facts', allowing you to dip into each issue, and each spread, as you need. Every issue contains a series of 'real voices' – interviews with people whose lives are affected and shaped by the topic in question. Whether you want to stimulate debate, to provide up-to-date, scientifically accurate examples around particular issues, or to get across complex ideas to your students, *Big Picture* helps you to bring cutting-edge science into your classroom.

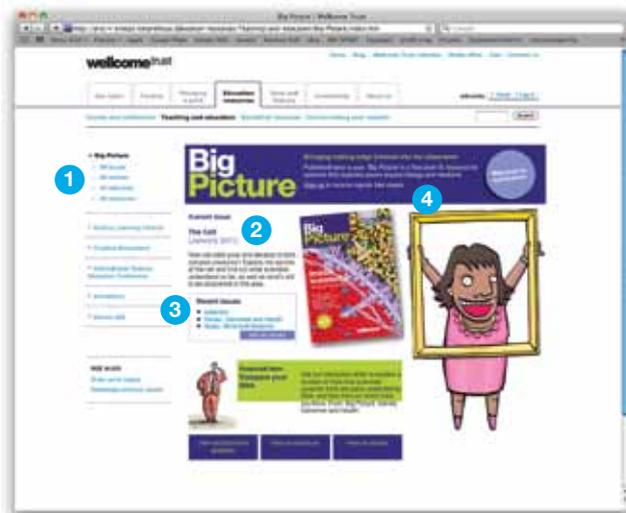


- 1 Title** – Each spread deals with a particular aspect of the title topic.
- 2 Intro** – This sets the scene for the spread within the issue, and the wider world.
- 3 Article** – Each article can be used alongside others from the same spread or the rest of the issue, or as a standalone component for a lesson.
- 4 Image/diagram** – Illustrations and diagrams help you express complex ideas in a visual way, as well as helping to place the issues in question into a real-life context.

How to use the *Big Picture* website

As well as twice-yearly magazines, there's loads of other useful material available on the *Big Picture* website (www.wellcome.ac.uk/bigpicture). The exclusive online content is created for each issue, and includes articles, videos, games, image galleries, animations, lesson plans, activities and more. Our selected links help you and your students to get the most out of the web for each topic.

Also on this site, you can download PDFs of the current and all 13 past issues of *Big Picture*. There are also curriculum-matching details, and info on how to order copies of the magazines.



- 1 Left-hand menu** – Browse *Big Picture* online by title, article, activity or resource.
- 2 Current issue heading** – Explore the online content for the latest issue.
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Introducing the cell

Join us as we explore the building block of life.

The cell is the smallest unit of life. Some simple organisms consist of just one cell, whereas more complex beasts, like us, have vast numbers of them. Humans are among the organisms built up from eukaryotic cells, which have their DNA parcelled up in a nucleus, and lots of subcellular compartments, called organelles. Prokaryotic organisms (such as bacteria) are simpler: cells still with DNA, but having no nucleus or membrane-bound structures. The vast majority of these are unicellular, while most

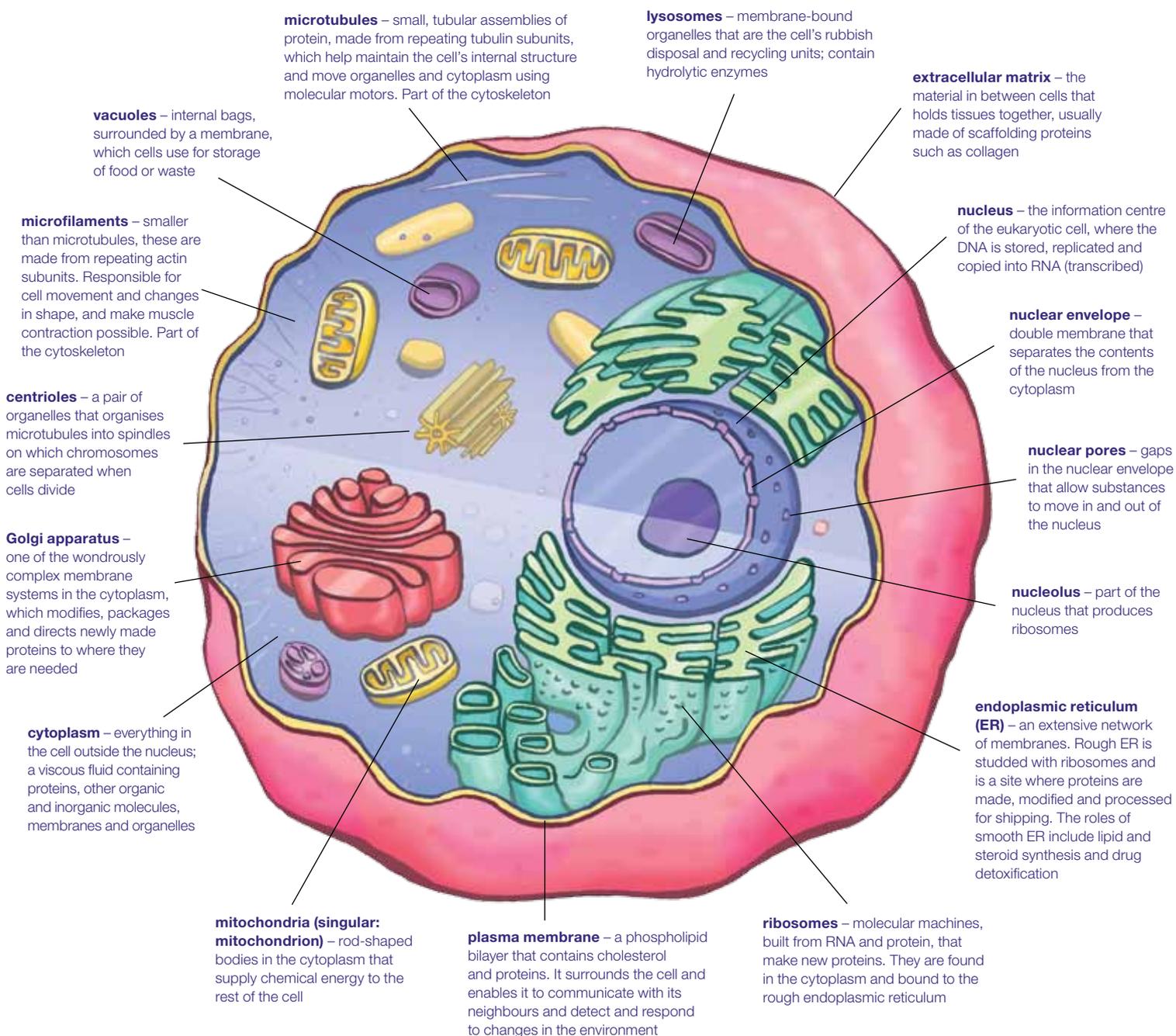
eukaryotic organisms are multicellular.

The intricately organised insides of eukaryotic cells allow them to have different things happening in different compartments. Keeping a cell going depends on getting the right molecules to the right place at the right time. Having distinct spaces does half the job, but it also requires sophisticated machinery to ensure the right things get into each section. Only material the cell has finished with, for example, can be allowed into a lysosome, where powerful enzymes

are poised to break down the material into smaller molecules.

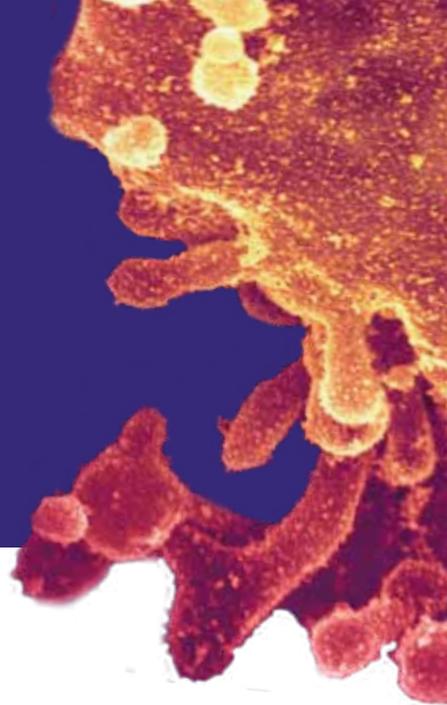
Cell theory was put forward in the 1830s, soon after the cell nucleus was first identified in eukaryotes. It recognised that living things are made of cells, that cells are the basic units of life, and that new cells are created by old ones dividing into two. Viruses – simple entities of genes and protein – need to get into a cell and hijack its cytoplasmic machinery to copy themselves. We describe these as acellular, and they are not considered to be living.

In this issue, we'll be focusing on animal cells – how they reproduce, grow, move, communicate and die. So join us to explore what we know – as well as what we still don't understand – about the cells that are the basis of all of us.



Beginnings and basics

Each of us has developed from a single egg and sperm to become a complex, sophisticated organism made of trillions of cells. So, how do cells divide, develop and work together to make this possible? And if each of our cells contains all of our genes, then how do they turn into different types of cell with distinct structures and functions? Why can't our cells go on dividing for ever?



The Golgi apparatus, which processes and packages proteins in the cell.

Dividing we stand

Cell division is a tightly controlled process.

The most complex thing a cell can do is to split into two identical cells. In actively reproducing cells, this begins with the copying of the cell's contents, including the chromosomes. The duplicates separate into different halves of the cell and then, during mitosis, the cell splits down the middle – and then the cycle starts again. A more complex type of cell division, meiosis, which generates eggs or sperm, has an extra stage. Each chromosome pair is separated, so that each cell has a single chromosome.

Seen under a microscope, the dance of the chromosomes looks magical, but it has a precise molecular mechanism. The movements of the chromosomes, like those of the cell, are controlled by microtubules. These are long tubes of protein subunits, which can assemble, break down and reassemble very quickly in a different arrangement.

Microtubules play a crucial role in mitosis, rearranging themselves from their usual place in the cytoskeleton to build a complicated machine called the mitotic spindle, whose other parts include motor proteins. The spindle grabs hold of the chromosomes and lines them up. It pulls the pair of chromatids that make up each chromosome in opposite directions so they end up in different halves of the cell.

The whole process is a carefully orchestrated sequence of movements involving hundreds of different proteins. A key component is the protein complex (two or more proteins that associate with each other) that assembles on chromosomes and provides a place for microtubules to latch on to, known as the kinetochore. Cell division is a very active area of research because it is one of the key cellular processes that goes wrong in cancer.

Seeing is believing

Cells were first seen over 300 years ago.

No one knew that cells existed before the invention of the microscope. Robert Hooke in 1665 saw spaces in dead sections of cork that he called 'cells', and the Dutch pioneer Anthony van Leeuwenhoek was astonished by living cells 20 years later. The insides of cells were observed much later, with more powerful light microscopes. Even the best light microscopes, though, can

only show objects larger than 0.2 μm (micrometres, millionths of a metre).

Electron microscopes can go smaller still. Today, they can even show how single molecules of newly made protein nestle inside the 'chaperone' proteins that help them fold up into their proper shape. Analysing images of hundreds of these protein complexes has shown just how they fit together. Understanding how proteins fold properly is important, because misfolded proteins can accumulate and cause diseases such as Alzheimer's.

Who's in control?

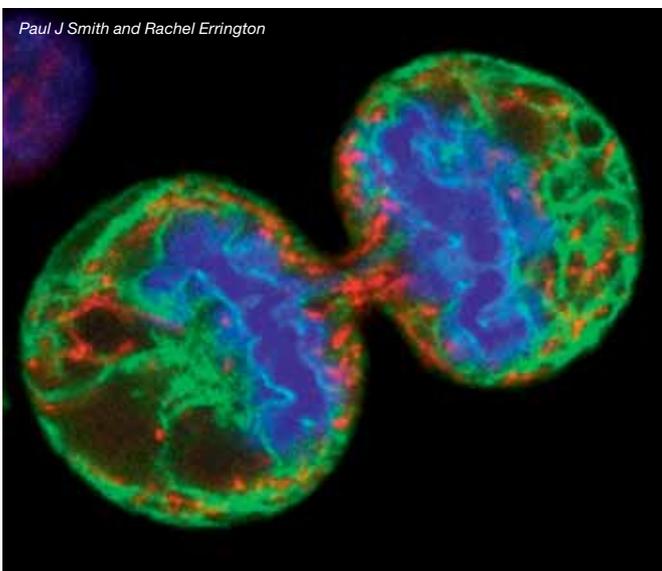
Your cells contain the same genome but different genes are in use.

The store of genes in the cell nucleus, the genome, makes your cells human. But every human has around 200 different cell types, each with an identical gene store. The differences lie in which genes are actually in use. Specific sets of genes are switched on and off as cells start to adopt specialised functions during development, a process called differentiation.

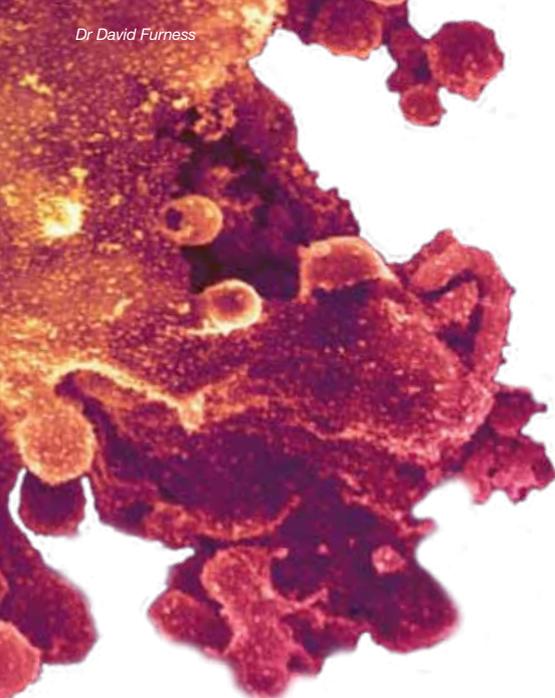
The genes, in turn, will generate unique patterns of RNA messages from reading the DNA that is in use, and a signature population of proteins and smaller regulatory molecules. These patterns change in response to gene signals, the contents of the cytoplasm and messages from outside the cell. The result is a complex developmental conversation. At one level, the

nucleus is in charge of the cell. But there is also a sense in which the cell, with its surroundings, is in charge of the information store in the nucleus, and how it gets used.

Scientists have decoded the entire human genome, but that does not give a picture of which information is active in any cell. This is registered in the transcriptome (the complete catalogue of messenger RNA molecules in a cell), and the proteome (the list of all the different proteins present). Unlike the genome, these are constantly shifting, so each is a snapshot in the life of the cell. How the transcriptome and proteome are tweaked by small changes in the cell's circumstances is one of the biggest topics in current biological research.



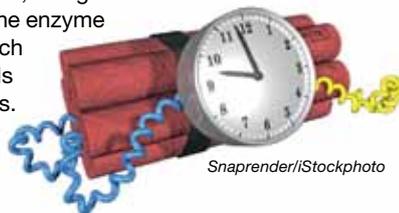
Human cancer (melanoma) cells dividing.



No limits?

Why don't our cells go on dividing for ever?

It is important to have just the right amount of cell division, so the process has lots of checks and balances. If the controls fail, there is a final limit. Each time a chromosome is copied, a repetitive stretch of DNA at its end, the telomere, gets shorter. The telomere is needed for the proteins that copy DNA to work properly, so when it is all gone there is no more chromosome copying, and no more cell division. In effect, telomeres count cell divisions. Human cells can normally manage between 40 and 60 divisions – this is called the Hayflick limit, named after Leonard Hayflick's 1965 discovery. Stem cells, and many cancer cells, can get round this limit using the enzyme telomerase, which rebuilds the ends of chromosomes.



Snaprender/iStockphoto

Inside the cell

How do things get around in the cell?

The inside of the cell is a scene of constant motion. Soluble molecules move around apparently randomly in the cytoplasm, but many components are transported more precisely. Many proteins are allowed only into one of the cellular compartments. Cells also have an elaborate network of fine protein filaments (strands), an interior cytoskeleton, which helps them keep their shape and provides the rails of a transport system. Small protein motors pull little bags, or vesicles, of cell products up or down microtubules or actin filaments. Special labels ensure the right cargo is sent to the right destination. These are usually proteins, or parts of proteins, sticking out of the vesicle.

The same system also moves organelles around or anchors them in place. The cell uses a lot of energy for all this transport, but it needs to speed things along. A protein molecule might take years to travel the length of the longest nerve cell by simple diffusion, but if it is bagged up and dragged along a microtubule it can cover 10 cm in a day. This is vastly more than most distances within cells, and means that even the ends of the long, drawn-out extensions of nerve cells, the axons, in your fingers or toes can be reached in a few days.



Exploring the matrix

Cells communicate with the matrix surrounding them.

Tissues contain cells and material between the cells. In connective tissues, like bone or tendon, this material – the extracellular matrix – predominates. In other tissues, it is distributed more sparingly. In all tissues, the cells and their matrix communicate, chemically and physically. The physical link is via proteins that cross the external membrane of the cell, which are known as integrins. One end of an integrin is tied into the cytoskeleton, the other to collagen fibres in the extracellular matrix.

The matrix also contains chemical messengers, often bound to gels made up of proteoglycans, a complex mix of proteins and the sugar-derived polysaccharides. These



C. Merrifield and M. Duchon

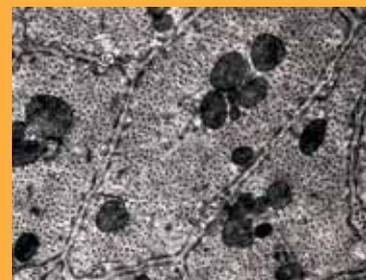
The filaments, coloured red, show part of the cytoskeleton.

include growth factors and signal molecules, which affect many processes, including cell migration. Some come from the cells that make the matrix, some from other cell types – and the cells, in turn, respond to the mix of signals as it changes over time.

One, two, or many?

Not all of your cells have a single nucleus.

Most cells have the standard single nucleus, but not all. Skeletal muscles, such as your biceps, have very long cells with many nuclei. They form by fusion of cells with one nucleus. Some cells in adult heart muscle have two nuclei. This happens because the cells take the normal cell cycle through copying and separation of chromosomes, but do not go the whole way and divide. Why does this happen? We don't know for sure, but one recent idea is that one nucleus lies dormant, but triggers further cell division if the muscle gets damaged. Red blood cells in mammals have no nucleus. For more on these cells, see page 10.



Prof. Giorgio Gabella

Transmission electron micrograph of smooth muscle cells.

Under development

Controlled cell division is a key part of development.

Perhaps the most remarkable fact in biology is that the several tens of trillions (1 trillion = 1 000 000 000 000) of cells that make you develop from a single cell – a fertilised ovum, or zygote. Controlled cell division is crucial for development. The dividing cells in the embryo are also differentiating and forming structures that fold, get reshaped, or even migrate to different locations. Disruption of one of the many genes involved in controlling all these subtle shifts increases the risk of developmental defects. The effects of these defects may be felt much later on in adult life, not just at birth.

FAST FACT

Human eggs are made in the embryo, so the egg cell that fused with a sperm to become you was actually produced around six months before your mum was born.



Yorgos Nikas

Cells and their surroundings

In any multicellular organism, cells don't exist in isolation. A cell's environment has a profound effect on how it develops, grows and functions, making effective communication between a cell and its surroundings – including neighbouring cells – vitally important. How do cells interact with their environment? What happens when these signalling systems are disrupted?

A society of cells

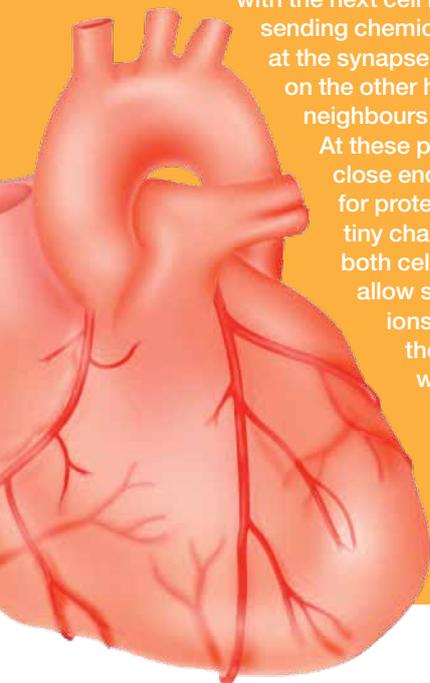
How do cells organise in an organism?

The human body is a closely organised community of cells. Tissues, collections of similar cells, work together in groups to form an organ. These organs work with each other in organ systems. The liver, for instance, is made up of 80 per cent of one kind of cell, hepatocytes, which make, store or secrete many proteins, fats and digestive enzymes. The remaining 20 per cent consists of several other specialised liver cell types, along with blood vessels, nerve cells and others. All have to work together for the liver to do its job. To keep the whole organism functioning correctly, most organs or organ systems also have to respond to the state of other organs, which may be a long way away.

For a smooth-running community, cells need good communication. They manage this in different ways, but all use either chemical or electrical signals. Nerve cells, for example, send electrical signals down their long fibres, but communicate with the next cell in the chain by

sending chemicals across a tiny gap at the synapse. Heart muscle cells, on the other hand, join to their neighbours via gap junctions.

At these points, the cells are close enough together for protein complexes with tiny channels inside to span both cell membranes, and allow small molecules and ions to pass between them. This allows waves of depolarisation to pass along a series of heart cells and keep the heart beating regularly.



Heart, showing the coronary arteries.

Cells within cells?

Were some organelles originally bacteria?

Some organelles inside eukaryotic cells look rather like cells themselves. Mitochondria – and the energy-generating chloroplasts in plant cells – even have a little DNA of their own. According to endosymbiotic theory, eukaryotes originated when symbiotic bacteria (which exist alongside cells in a mutually beneficial relationship) began to live inside larger cells, giving them ready-made compartments. Over time, these bacteria became permanent additions – chloroplasts and mitochondria – to the cells we see today.

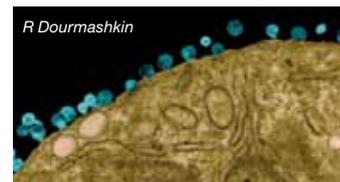
Researching membrane proteins

Why do researchers study membrane proteins?

Around one-third of all proteins are linked to membranes in some way. The ones that sit within the membrane are hard to study because pulling them out of their fatty surrounding often wrecks their normal structure. But examination of these proteins' structure and function shows how their roles in signalling can be exploited, either by viruses trying to bypass cell defences or by researchers developing drugs to treat disease.

One important focus for studies of membrane proteins is the action of HIV. The virus enters one kind of cell in the immune system by first binding to a normal cell surface receptor protein

called CD4. HIV has an outer envelope that can fuse with the cell membrane, allowing viral genes and proteins inside. Several other cell-surface receptors, and other chemical messengers, can help or hinder the fusion of membranes. Work on understanding exactly how they interact with each other suggests new targets for anti-HIV drugs.



HIV particles budding from the surface of a T cell.

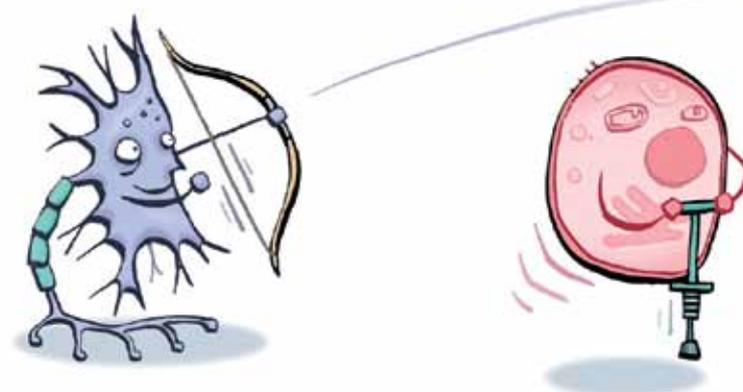
Passing on the message

Cells pass on signals via cascades of events.

Cells have evolved efficient ways of processing the many signals they receive. Many cell-surface receptors are linked to other proteins inside the cell. When the right molecule (the 'first messenger') from outside the cell binds to the receptor, it changes shape, and triggers changes in the internal protein as well. That in turn may activate an enzyme, most often one that makes the molecule cyclic adenosine monophosphate (cAMP), which is a messenger inside many cells. As cAMP is produced after this small but significant cascade of events, it is

known as a second messenger.

The effects of cAMP depend on both the first messenger (often a hormone) and the target cell. Several important hormones use cAMP as a second messenger. For example, adrenaline increases heart rate and how strongly the heart beats, as well as promoting glycogen breakdown in muscle. Different hormones whose actions are mediated by cAMP can cause the same response in a given cell – for example, adrenaline, glucagon and other hormones trigger the breakdown of triglycerides in fat cells.

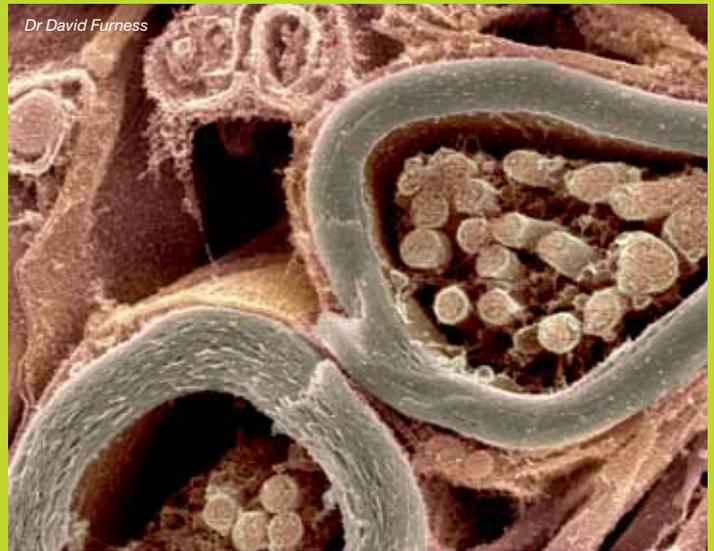


Communication breakdown

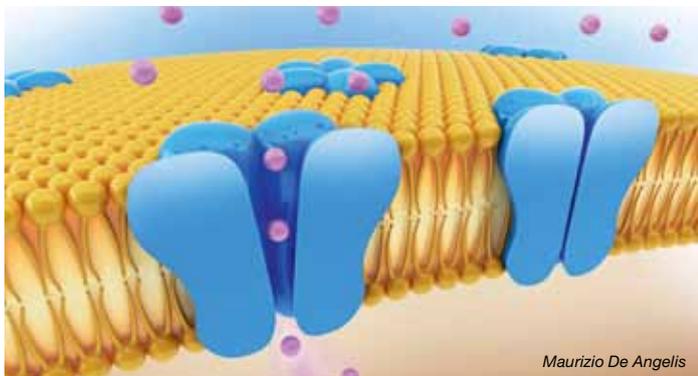
Problems in cell signalling can be bad news.

When messages between cells are blocked or scrambled, there are usually harmful results. Autoimmune diseases, in which our own immune cells attack body tissues, are partly due to errors in identifying cells. In multiple sclerosis, misdirected T cells remove the insulating sheath around nerve fibres, while tumours begin when cells ignore messages telling them not to replicate, or when they misread signals to keep dividing. Teratomas (tumours that can contain hair, teeth and bone) arise from germ cells (sperm and eggs) that are triggered to begin dividing inside the body.

Some diseases affect cell–cell signalling directly. In Alzheimer’s disease, toxic clumps of a protein called amyloid appear in the brain. They build up from fragments of a precursor protein present at synaptic junctions, which is abnormally processed. Another example, whose full details are still being worked out, is diabetes. In type 1 diabetes, sugar metabolism gets out of control because the cells that make the hormone insulin die off. In the more common type 2 diabetes, there is insulin in the circulation, but the cells that normally respond to it are deaf to the signal.



Colour-enhanced image of two myelinated nerve fibres.



Ion channels in the cell's plasma membrane.

Mind your membranes

Membranes are important inside and around the cell.

The cell's plasma membrane separates inside from out and allows communication. Its structure is based on a foamy bilayer of phospholipid molecules, but it is studded with proteins that regulate the traffic back and forth. Some just make pores that allow small, soluble molecules to get through. Some use energy to move their chosen cargo more actively from one side to the other. Other membrane proteins bind signalling molecules, such as hormones, that float by outside, and then pass a message to the interior.

When larger quantities of some substances need to be moved from cell to cell, they are bagged

up into membrane-bound sacs called vesicles that can fuse with the cell membrane. As usual, the vesicles are tagged with special proteins that label the contents, and interact with yet more membrane proteins to make sure the correct cargo is delivered.

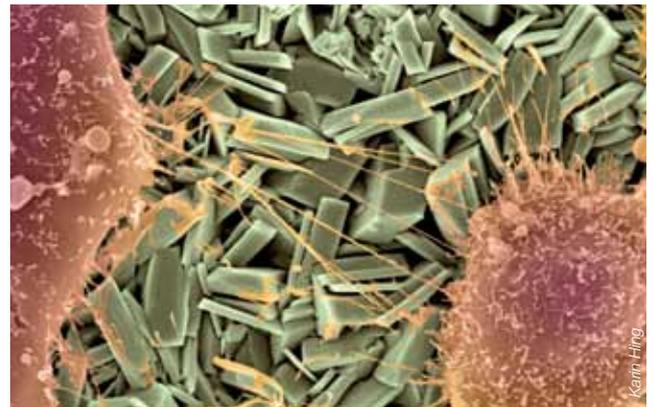
The same system operates for internal transport between the cell's compartments. Vesicles bud out from one membrane, then fuse with another. Recent work at the University of Cambridge has shown how a mutation in protein complexes that regulate vesicle transport can cause a rare genetic disorder that leads to albinism, impaired lung function and chronic bruising.

Don't stop moving

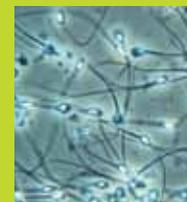
How and why do some cells move?

One simple response to a signal – for a few cell types in adults at least – is to get moving. Cells can move slowly by crawling or sliding along, aided by changes in the cytoskeleton, but faster movements depend on specialised external organelles. Motile cilia are small projections that wave or beat and either propel a cell through a fluid or waft the fluid past a line of cells, as happens when mucus is cleared from your windpipe. The larger flagella are used only to move cells. The long, whip-like tail of a sperm cell is an important example. Research on how its movement is activated, and how it changes when a sperm gets close to the surface of an egg, may help overcome some causes of infertility. It could also pave the way to an effective male contraceptive.

Cell movement is also an important part of wound healing. A gash in the skin triggers new mitosis around the edges and also induces cells to move into the wound space to begin covering the opening.



Two human bone-forming cells (osteoblasts) crawling over ceramic crystals.



FAST FACT

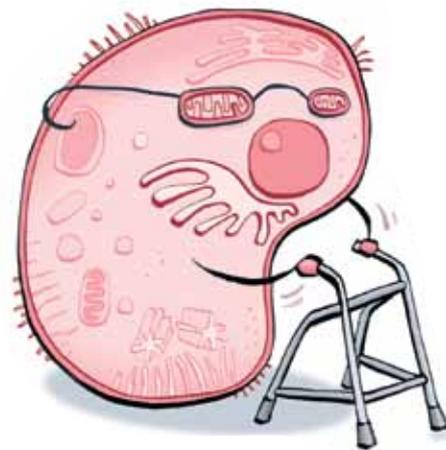
A man makes 1500 sperm per heartbeat

Source: *Science* 328(5974):15.

Joyce Harper, UCL

A matter of life and death

Cells have very different lifespans. While some cells stay with us for our whole lifetime, others have fleeting, single-day roles as part of our bodies. For example, while men produce sperm throughout their adult lives, women are born with all their eggs – how might the age of a woman and her eggs affect any potential offspring? Proper recycling and breakdown of a cell’s unwanted parts is necessary to keep things in working order. So how do cells dispose of their waste and – when cells actually die – themselves?



The life expectancy of the cell

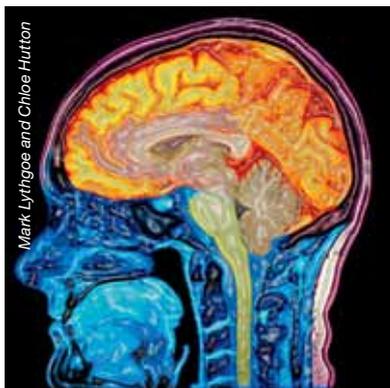
The lifespans of different cells vary greatly.

Cells can last a human lifetime, but not many do. Some, such as the white blood cells that hunt down bacteria, are gone in less than a day, while cells in the lining of the gut hang around for nearly a week. Most, though, last a good deal longer – liver cells for a year or so, bone cells for perhaps ten years.

Ten years, in fact, is about average. Just a few kinds of cell can endure from birth to their owner’s death. They include cells inside the

lens of the eye, which become inert once they are in place in the embryo, cells in heart muscle and, perhaps most importantly, neurons in the brain (see below).

Counting all the cells a person ever has would take several lifetimes. The average turnover of all human cells in different tissues is seven to ten years, so the lifetime cell count is perhaps ten times the adult total (at least several tens of trillions of cells). That ignores a lot of other cells, like the 180 or so types of bacteria and other microorganisms that live in and on our bodies. It’s thought that each of us carries ten times as many of these cells as we have our own, human cells.



Magnetic resonance imaging scan of the head.

Building your brain Can we grow new nerve cells in our brains?

Some organs, such as the liver, can regenerate if they are damaged, and will, within limits, grow to cope with demand. Exercise your muscles in the gym, and they get larger. Sadly, this will not work for your brain: although ‘exercising’ your brain may alter cell–cell connections, the number of neurons will not change.

Or will it? There is controversy about whether the brain can grow new neurons, especially in the cerebral cortex, home of advanced thinking skills. If so, the numbers

are small. The vast majority of neurons in the brain of the oldest man or woman have been there for their entire lifetime.

It was discovered in the 1990s that the hippocampus, where new memories form, can produce new neurons late in life. Since then, evidence has mounted that stem cells that make extra neurons are found in the cerebral cortex as well, at least in mice and monkeys. If further work confirms this finding, researchers will want to know whether the cells can be activated, to help heal injuries such as stroke or even, perhaps, improve brain function.

New cells for old

The age of eggs and sperm can be very different.

Men produce sperm continually after puberty, and dispose of old ones after a couple of months. Human eggs (ova), on the other hand, are made in the embryo, and released from the ovaries much later on. Actually, these are primary oocytes, which have not completed meiosis. After puberty, one oocyte a month matures into a secondary oocyte, which can then be fertilised.

The older a woman, the older her eggs, and the greater the chance that she will have a baby with chromosomal abnormalities. Serious chromosomal problems may lead to miscarriage, so older women are at greater risk of this than younger women. Very recent studies indicate that there are stem cells in mammalian ovaries that can produce new egg cells in adults. This might help to treat infertility, or to reduce risks of some birth defects.





Human chromosomes.

Getting on a bit

Ageing cells have a number of tell-tale signs.

Over time, the waste disposal can get clogged up. Old, tangled proteins and other cellular junk defy the lysosomal enzymes. Remnants of fatty acids are a particular problem and they make up a big portion of the yellowish pigment granules known as lipofuscin, whose appearance is a sure sign of an ageing cell. Other signs of cell ageing, such as

shortening of the telomeres on the ends of the chromosomes, are related to how many times the cell has divided. Most, though, are the result of normal wear and tear. Mitochondria age faster than other organelles. Their job of energy production exposes them to reactive chemicals – free radicals – that can damage DNA. Mitochondria have some essential genes in their own DNA, and the proportion of them that have serious defects increases as the person, and their cells, grow older.

Waste disposal

How do cells dispose of their unwanted parts?

Cells are continually making new molecules, while old ones are broken down and recycled. The main site for this is the lysosome, which acts as a cellular stomach. A typical human cell has about a hundred lysosomes, each a collection of potent hydrolytic enzymes, which break down substances, enclosed in a membrane. Old organelles, other cellular waste and, in immune system cells, old red blood cells or bacteria swallowed by the cell are all wrapped in membranes of their own. These then fuse with the lysosome, where they are quickly broken down into small molecules for re-use.

In cases where one of the lysosomal enzymes fails, the cell cannot keep up with removing waste. In the rare genetic condition Tay–Sachs disease, for example, an enzyme that mops up a fatty chemical in neurons is defective. The

chemical, a ganglioside, accumulates and eventually destroys cells in the brain and spinal cord, causing a progressive loss of mental and physical function that usually results in death before the age of five.

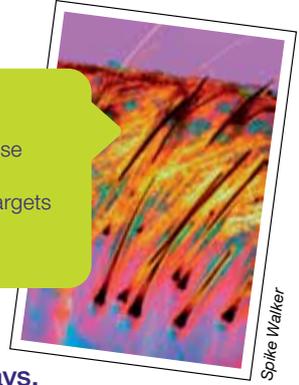
The right packaging is also crucial for recycling and disposal. Cells constantly pinch off bits of outer membrane, turning a small pit in the membrane into a vesicle, which is brought inside. Larger vesicles import material from outside. The vesicles then fuse with an extensive network of tubes and bags, known as endosomes, which sort incoming material. New vesicles bud off from here, and shift designated contents onward – to other parts of the cell, back to the outer membrane or to the lysosomes. Cell surface receptors are recycled as part of this process, too.



FAST FACT

Chemotherapy can lead to hair loss because the hair follicle epithelial cells – like cancer cells – divide rapidly, and hence are also targets of many anticancer drugs.

Source: *Scientific American*, 5 January 2001.



Spike Walker

So long, cells

Cells die in a variety of ways.

Cells, like people, die if they are starved or poisoned. Blockage of an artery leading to the heart causes death of heart muscle cells in a heart attack, for instance. A similar obstruction in the brain leads to the destruction of brain cells in a stroke. This kind of death is called necrosis. But a cell's life can also end in other ways.

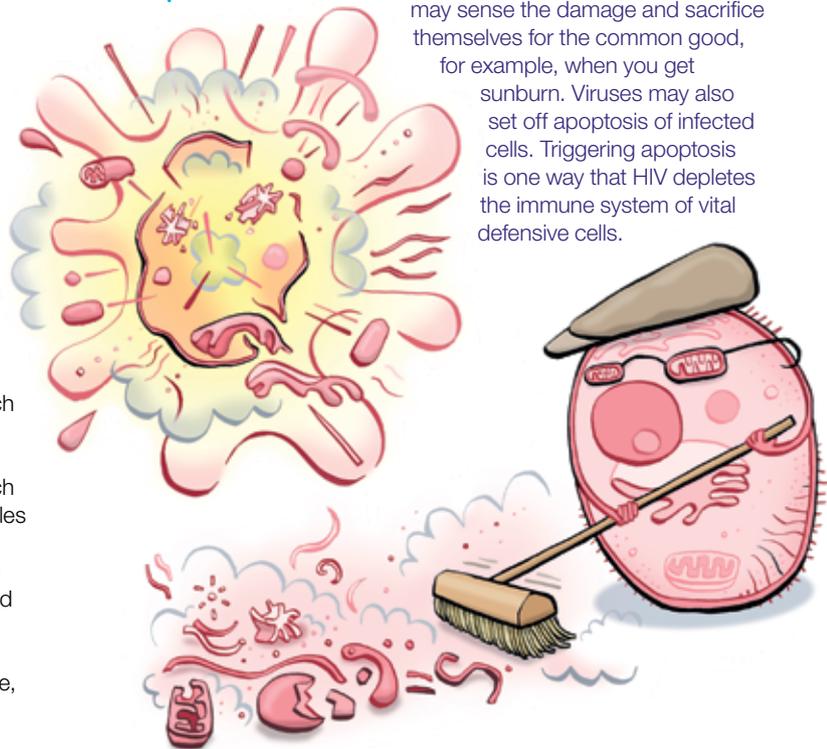
One, whose importance only became clear recently, is programmed cell death, or apoptosis. Cells have an inbuilt self-destruct routine that keeps them poised on the brink of suicide. Normally, signals from neighbouring cells keep them from doing themselves in, but if the signals change, the cell pushes the suicide button.

This is a neat and tidy death. While necrotic cells swell and burst, spilling lysosomal enzymes and damaging surrounding cells, apoptosis involves the orderly dismantling of organelles and proteins, while the cell shrinks and ends up as a few vesicles, which are cleared up by other cells.

Apoptosis happens in different places at different times. The developing embryo uses it to sculpt fingers from a web-shaped hand, by removing the cells in between the fingers. Cells with damaged DNA

may sense the damage and sacrifice themselves for the common good, for example, when you get

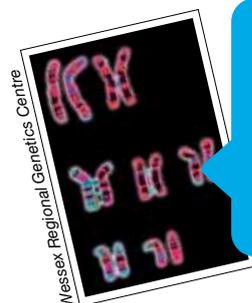
sunburn. Viruses may also set off apoptosis of infected cells. Triggering apoptosis is one way that HIV depletes the immune system of vital defensive cells.



FAST FACT

The 2009 Nobel Prize in Physiology or Medicine went to Elizabeth Blackburn, Carol Greider and Jack Szostak for their work on how chromosomes are protected by telomeres and the enzyme telomerase.

Source: www.nobelprize.org



Wessex Regional Genetics Centre

Stem cells and development

Stem cells are very special – not only can they renew themselves but they can also become differentiated cells. Stem cells found in an embryo can become any of the cells found in the body and, as such, hold great promise for generating replacement tissues and cells to treat a number of diseases and disorders, including diabetes, Parkinson’s disease and multiple sclerosis.

Stem cells

What do we mean by stem cells?

If a differentiated cell divides, all its descendants will be identical to it and each other. A stem cell can do more, producing stem cells and differentiated cells. They’re also self-renewing, which means that they can go on and on dividing.

Stem cells vary in their potency – how much they can differentiate. A newly fertilised egg and the products of its first few divisions are made of totipotent cells. These cells can give rise to any cell type in the body, including the placenta, and so can produce a whole organism. Embryonic stem cells, a few steps beyond the egg in development, are pluripotent – they can become any type of specialised cell, but not a whole organism. Multipotent cells, which can make just a few types of cell, include those in bone marrow that can generate red or white blood cells. Most adult stem cells (those found in differentiated tissues and organs) are multipotent. Unipotent cells, such as those in the skin, make just one fully differentiated cell type, usually where lots of new cells are needed regularly.

A lot of research focuses on the transitions between these states. A basic question is whether pluripotent cells carry on as they are by default, or need some continuing signal to remind them to stop differentiating. Research strongly suggests that embryonic stem cells are self-sustaining, and keep making more stem cells, as long as they receive no signals from a particular protein that triggers cell differentiation.



You seem different...

How are cells specialised for their roles?

Each cell type is specialised for the role it plays; specific characteristics range from making key proteins to general properties like shape. Red blood cells, for example, are small biconcave discs. This shape gives a large surface area, helping the cells to ship oxygen from the lungs to the tissues, and a little of the carbon dioxide the other way.

The shape also gives flexibility, helping the cells squeeze through the smallest capillaries. Developing red blood cells begin with a nucleus and organelles, but lose them before they start work, which in effect reduces the cells to bags full of haemoglobin, the protein that carries oxygen and carbon dioxide. If the shape is distorted, disease can result. For example, in the inherited disease sickle-cell anaemia, some red blood cells become sickle-shaped owing to abnormal haemoglobin molecules clumping together.

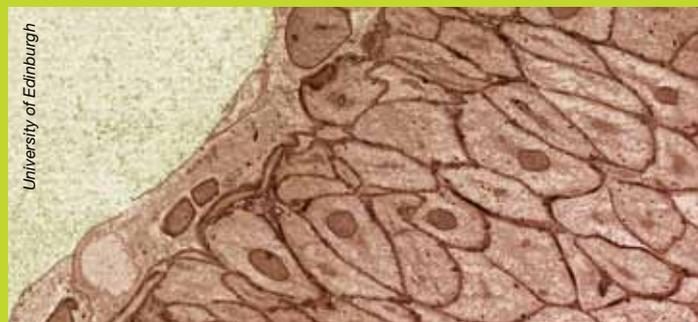
Organs often contain sub-populations of cells. The pancreas, for instance, makes a

range of hormones and digestive enzymes. Small regions of the pancreas known as the Islets of Langerhans contain four different cell types, which each make different hormones. The most common cells there – beta cells – make insulin and amylin.

How do cells specialise? A stem cell will receive a signal from its surroundings that triggers a change in the pattern of genes that are turned on and off, directing the cell towards a more specialised state. Having a detailed understanding of these changes and how they are triggered may allow us to control them.



Sickled and normal red blood cells.



Transmission electron micrograph of epithelial (skin) cells.

This way up

Direction is important in cells’ development and function.

A cell’s development – including its direction – is constantly influenced by the cells surrounding it. An epithelial sheet, for example, is asymmetric. One face – the apical surface – is exposed to the watery contents of the gut, or to the air in the lungs. The opposite face – the basal surface – sits on supporting layers of collagen and connective tissue. Cells that secrete molecules into the gut need different membrane proteins at the top and bottom, and so do those specialised for

absorption. The cell keeps track of which end is which, so that molecules go the right way.

A more complex example is found in the ear, where a type of epithelial cell in the inner ear turns vibrational signals into electrical messages so we can hear. These hair cells, which have a bundle of fine cilia, have a top and bottom, but have to be arranged in the right direction along another axis as well. If they lose this orientation, or planar polarity, the sense of hearing may be impaired.

Using stem cells

Stem cells hold great potential for treating disease.

If we can learn how to control the differentiation of stem cells we might be able to remedy many kinds of cell damage in the body. Embryonic stem cells are pluripotent, and so the most versatile, but their use is not without controversy (for more, see pages 12–13).

Some pharmaceutical companies use stem cells to test new drugs. Stem cells

for studying specific diseases – including Huntington's, Parkinson's, muscular dystrophy and type 1 diabetes – have been made by reprogramming adult cells from patients into a pluripotent state. Pluripotent stem cells would give researchers the chance to test drugs on different types of cell, but only if they can develop ways of controlling how and when these stem cells differentiate.

Adult stem cells (those found in differentiated tissues and organs) are potentially useful too. Researchers in Cambridge, for example, are using single adult skin stem cells to explore the biological signals



Annie Cavanagh
Scanning electron micrograph of embryonic kidney cells.

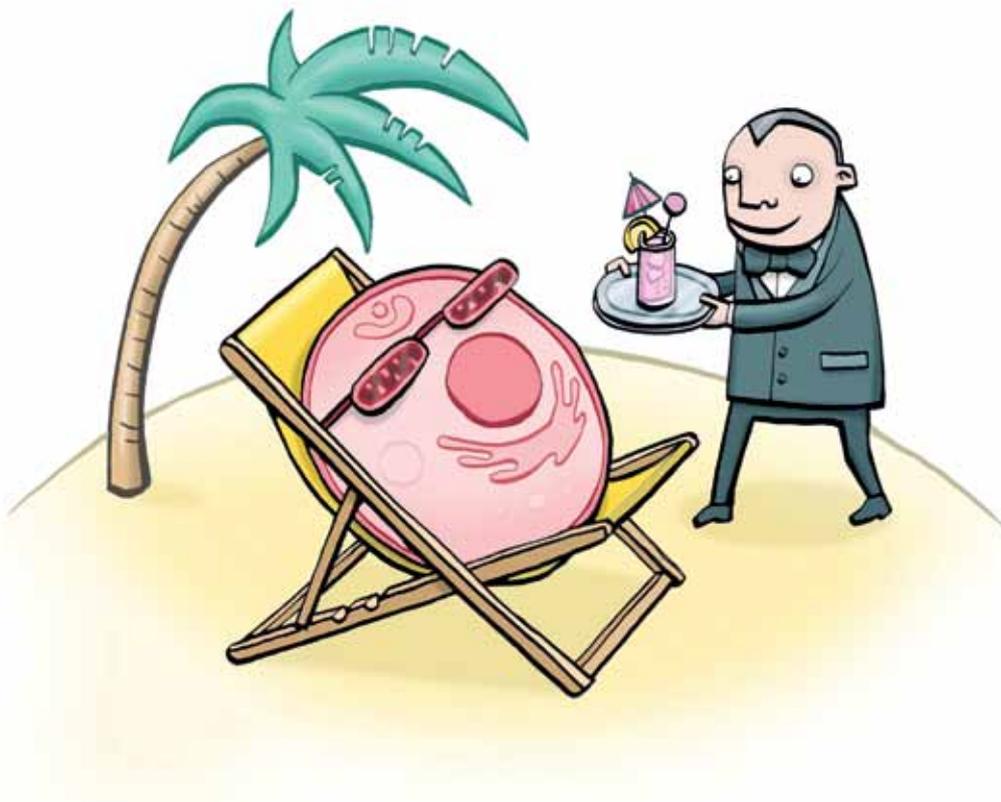
involved in cell differentiation. This approach can also be used to screen drugs for, in this instance, repairing damaged tissues.

Getting some culture

Many types of cell are grown in the lab for research.

Many kinds of cell can be kept alive outside the body in a laboratory dish. If they grow and reproduce, you have a cell culture. Many cell culture 'lines' (or types) are used in research. To some extent, they can substitute for whole organisms, particularly for animal testing of toxicity or drug effects. However, cultures usually consist of a monolayer (a layer one cell thick) of a single type of cell, not the mix of cells found in real tissues. They also lack the three-dimensional structure of tissues and organs, which have defined shapes and support their cells in carefully ordered arrangements.

Successful tissue culture is as much art as science. Cells need carefully controlled conditions to grow, including the right temperature, gas mix and growth factors in the medium they grow in. The longest-lived cultures often derive from cancer cells, which have found ways to override normal controls on cell division. Such cell lines have to be checked continually. The cancerous cells may go on changing, as they do in a tumour that's still in the body. It is also easy for cultures to become contaminated by other cells. If this goes unnoticed, experiments may not be testing what the investigators think.

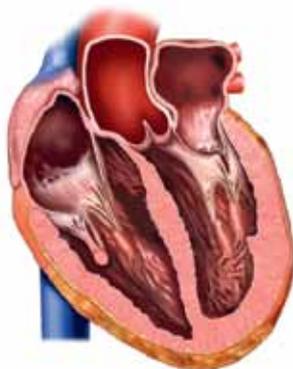


More, and bigger

Organs can grow by getting more cells, or larger ones.

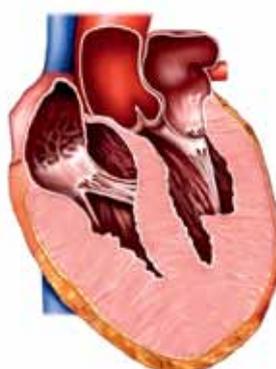
An organ can grow in two ways. Adding more cells makes it bigger. But so can increasing the size of individual cells (called 'hypertrophy'). We use both methods. The embryonic heart increases in size by adding extra cells, but after birth, our hearts grow by hypertrophy.

By exercising, we stimulate this process, and the hearts of athletes can grow much larger still. This so-called physiological hypertrophy is normal; when you stop training, your heart will adapt and slowly reduce



Normal heart (cut section).

again. In heart failure, which can result from many things such as infection, poor diet and high blood pressure, there is an increased load on the heart that

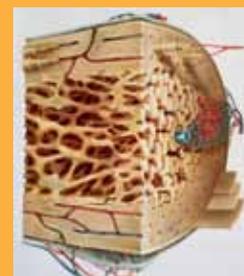


Heart muscle becomes too thick (hypertrophy).

stimulates hypertrophy. In this case, despite the increase in size, heart performance actually worsens.

FAST FACT

Stem cell therapies are already in use in the form of bone marrow transplants – the first of which was performed in 1956. *Source:* www.biotechlearn.org.nz



Cross-section of bone.

Stem cells and the future

Advances in stem cell technologies are occurring rapidly, bringing with them different ethical, moral and social questions to consider. Take a look at the timeline and the three scenarios below to explore your thoughts on the sources and use of stem cells in medicine and human enhancement.



Umbilical stem cells

Many of the embryonic stem cells used in research in the UK come from fertilised eggs donated by people undergoing *in vitro* fertilisation (IVF). They decide how any 'excess' embryos from these procedures are used, and can choose to donate them to research. The use of embryonic stem cells is controversial and opponents argue that destroying embryos to remove stem cells is inhumane. Using umbilical cord stem cells is an alternative source, potentially with fewer ethical concerns.

Cord blood stem cell transplants have been used to help people with diseases such as leukaemia and lymphoma. However, if the donor and the recipient are not genetically similar enough then donor cord blood can be rejected by the patient. This is less likely to happen than during bone marrow transplants, though, and as cord blood banks grow, there will be a greater chance of finding suitable matches.

In 1978, blood stem cells were discovered in human umbilical cord blood. At first it was thought that cord blood stem cells were only able to differentiate into types of blood cell, but research now suggests that they may have greater potency than this.

Scientists in the USA have used human umbilical cord stem cells to treat mice with thin, cloudy corneas. The stem cells were shown to take on the properties of cells in the cornea of the eye, showing the potential of this research to help those with loss of vision.



"It was easy to donate my cord blood and I hope that one day the stem cells in my sample will help someone who needs them."

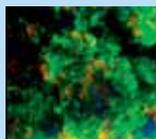
"I don't feel comfortable donating my umbilical cord blood – who knows what they might be able to do with it in the future?"

Question: Should it become obligatory for women who give birth to donate their umbilical cord blood for research?



Snapshots of the stem cell story

- **1958:** Leroy Stevens identifies pluripotency of certain mouse cells



Wellcome Trust
Sanger Institute

- **1996:** 'Dolly the sheep' is the first mammal to be cloned by somatic nuclear transfer – adding a nucleus from an adult sheep cell to an unfertilised egg with the nucleus removed



Pr Plially/Eurellos/
SPL

- **1998:** Scientists at the University of Wisconsin isolate and grow the first stem cells from human embryos left over from IVF



K Hardy

- **2004:** Britain opens the world's first government-financed stem cell bank, containing embryonic and stem cell lines



- **1981:** Scientists successfully culture (grow) pluripotent mouse embryonic stem cells

- **1990:** Human Fertilisation and Embryology Act passed in the UK, includes founding of Human Fertilisation and Embryology Authority, which regulates the creation, use and storage of human embryos in treatment and research

- **2001:** UK Parliament rules embryonic stem cell research can occur using government funding. Human embryos can be created for research purposes only, but not kept beyond 14 days

- **2006:** Korean scientist Woo-suk Hwang found to have fraudulently claimed the creation of human embryonic cells through cloning

Admixed embryos

Another way to avoid using human embryonic stem cells could be to create hybrid embryos, by removing the nucleus from an animal's egg and replacing it with a human body cell nucleus. The egg is not fertilised, but is triggered to develop with a jolt of electricity. If it works this could lead to early embryonic cell division, and production of human stem cells. However, the absence of the regulatory chemicals present in a human egg makes such work tricky to accomplish.

Since 2008, three research groups in the UK have been granted licences by the Human Fertilisation and Embryology Authority (HFEA) to create cytoplasmic hybrid embryos for research. Human admixed embryos are not allowed to develop beyond 14 days, it is prohibited to implant them into humans or animals, and their use is regulated by the HFEA.



"I'm really excited about being able to use hybrid embryos. Working with stem cells created this way will help me to research genetic neurodegenerative disorders such as Alzheimer's and Parkinson's."

"It seems unnatural to be mixing up animal and human cells. How do we know the long-term effects of this?"

Question: Is creating a human admixed embryo from a mature human cell and an animal egg cell for research more acceptable ethically than using a human embryonic stem cell?



Induced pluripotent stem cells

Now, consider a future where researchers have discovered how to 'reset' adult stem cells and give them pluripotency, without a danger of them becoming cancerous when introduced into the body (so induced pluripotent stem cells – IPS cells – could be readily produced in the lab). See below for the type of advert that this could lead to.

PLURI-U

PUTTING THE 'I' INTO IPS CELLS!

Transplants from donors are a thing of the past, thanks to Pluri-U. Simply attend your local clinic and have a small skin sample taken. Then, technicians will treat your cells with the right combination of chemicals and produce whichever cells you need for your condition, tailor-made to match your own immune system. No rejection! No immune-suppressing drugs!

But don't take our word for it!

Marion, 41, says: "A lifetime of type 1 diabetes, and my disease was gone after one procedure. No more insulin, no more monitoring my blood sugar! My only regret is that this wasn't available 20 years ago!"

Mark, 35, says: "Our son was born with sickle-cell anaemia, but thanks to Pluri-U's cell reset and gene therapy package, his blood cells are now normal and he's disease-free!"

Question: What about using stem cells to enhance humans – do you think it would be acceptable to use the same technology to make you stronger or able to run faster?



- **2006:** Dr Shinya Yamanaka (below) and Dr Kazutoshi Takahashi create and name the first 'induced pluripotent stem cells' by treating mouse skin cells so they become like embryonic stem cells



Rubenstein/flickr

- **2008:** The second UK Human Fertilisation and Embryology Act passed, amending the 1990 Act, allowing researchers, under tight controls, to create animal-human hybrid embryos by replacing the nucleus from an animal egg with a nucleus from a human body cell



Domino/stock.xchng

- **2009:** An international team of researchers creates the first human induced pluripotent stem cells without using viruses



Maurizio De Angelis



See www.wellcome.ac.uk/bigpicture/cell for a lesson plan to use with these articles.

- **2007:** A Japanese team including Yamanaka and Takahashi and a separate US team create the first induced pluripotent stem cells from human cells

- **2008:** Scientists at the Harvard Stem Cell Institute create stem cells for ten genetic disorders, which will allow researchers to understand better how diseases develop in cultured cells

- **2010:** In the USA, a patient with spinal cord damage becomes the first person in the world to be injected with embryonic stem cells in the first official clinical trial of this therapy, in humans, which will test if it's safe and if it works

Real voices

Three people talk to us about the role of cells in their lives. Meet Spike Walker, an award-winning micrographer, Olly Rofix, who was diagnosed with a rare form of leukaemia in his early 20s, and Andrew Evered, whose job as a cytologist means he screens cell samples for cancer.

Spike Walker

Micrographer
(takes photos through microscopes)



When did you first get into microscopy?

When I was 11, a friend of mine told me there was a microscope at his school. So I asked my father for one. He was on about £2.50 a week but he bought me one for £4.50. And it's been an interest for 65 years now.

What has kept your interest so long?

It's an entirely different world. And it's accessible. People will spend a lot of money going out to Kenya to see lions in the wild. I can go up the lane, and take a tubeful of dirty water out of one of the ditches and I've no idea what I'm going to see, out of possibly 30 000 species. A lot of them are single cells, and they're absolutely fascinating. The average cell in your body does one thing. If it's a muscle cell it spends its time contracting, for example. These cells living on their own in water, and do everything: they propel themselves about, catch their prey, digest it and excrete the remains, and find a mate.

Which cell do you find particularly fascinating?

There's a one-celled animal called a perenema. It's a very elastic, transparent sack with a stout whip sticking out the front end of it, which propels it around. The very tip of it wiggles like a nose. Sometimes I'm looking at something else in a drop of water, and suddenly one of these twitchy little fingers appears in the corner of your eye, followed by yards of

nothing and then, unbelievably, this sack-like body. There are times I've nearly fallen off my chair laughing.

What's tricky about making images with a microscope?

If you're making a portrait of someone, you can decide exactly where your subject is going to sit. And other people hopefully don't come rushing in and out and getting involved in the photography. But if you're photographing things in dirty water, other things will be there and they'll swim in and out. Or the dancer you're photographing won't keep still and keeps moving out of the frame.

What's your favourite image?

There's one of oxidised vitamin C that got a Wellcome Special Award of Excellence in 2008. I made it by scratching boxes on the slide with a needle. The crystals grew in the boxes, and the image looks like a Victorian wall decoration – little boxes with shells inside.

What awards have you won?

I've won 19 Wellcome Image Awards since I started entering in 2002. This year I won the Royal Photographic Society's Combined Royal Colleges Medal – probably for being the oldest micrographer still in existence!

For a video on Spike and his work, see www.youtube.com/watch?v=Xo7mr90GYLA

Olly Rofix

Sailor and bone marrow recipient



Nick David

What do you do?

I'm 25, I used to be an engineer at the port of Felixstowe, but I left work last year to concentrate on rebuilding my boat. I bought it as an inspiration to get me through the bone marrow transplant I had for leukaemia five years ago.

What are your plans next?

Next year I'm sailing around Britain to raise money for the Anthony Nolan charity. They run the UK's largest stem cell register. They found me my donor and saved my life. I also want to show other young people with cancer that if you've got a focus or a goal, you can live longer, or you can beat it.

How did you find out you had leukaemia?

I was first diagnosed in 2005 with glandular fever because I started to get very tired. Then a routine blood test showed that I had leukaemia. The doctors told me I was only the third person in the world to be diagnosed with this type of leukaemia – and the other two were dead. So I needed a bone marrow transplant urgently. Anthony Nolan scanned the register and found me one with a really good tissue match.

How did they give you the transplant?

I had to have another lot of chemotherapy and total-body radiation – the harshest form they

ever give to anyone – to destroy my own bone marrow. Then they gave me the new bone marrow. It just dripped in from a bag like a blood transfusion, through a tube that went directly through my chest muscle and ribs into my heart. It took about two hours for the bone marrow to drip in. As I watched it dripping in, I was thinking, whose blood is that? Who is this one person in the world who's saving my life?

How did you understand the stem cell therapy?

I saw it in an engineering way, as giving me an oil change: getting rid of my bone marrow and putting fresh in.

Did the doctors tell you what your prognosis was?

Yes, the survival rates of the transplant then weren't fantastic, 10 to 15 per cent. It was quite scary – your whole life is put into a figure. Now, I'm in remission, and if I get the all-clear next March, that will be five years post-transplant.

Did you meet your donor?

Yes, earlier this year. I met him and was able to thank him, as I wouldn't be here without him.

Find out more at www.olivers-travels.co.uk. If you want to become a bone marrow donor, join the Anthony Nolan register – visit www.anthonynolan.org.



makeanotherme/istockphoto

Andrew Evered

Cytologist
(screens cells for cancer)



What do you do?

If you go into my cytology lab you'll see lots of people looking down microscopes. They don't look very busy, they're not moving around, but their brains are working overtime. They're looking at human cells on glass slides that have been stained with dyes so we can see them better.

What cells do you look at?

Some 90 per cent of the screens we do are cervical, for the UK's Cervical Screening Programme. We decide if they are normal and healthy, or pre-cancerous. The other 10 per cent are non-gynaecological screens of cells in body fluids: sputum, urine and chest drains and so on. We're looking for signs of other cancers, such as lung or bladder cancer.

How can you spot a pre-cancerous cell?

Through changes to the nucleus. In pre-cancerous cells or cancers – they're all on a spectrum – the nucleus loses its roundness, becomes irregular in shape and gets larger. It also increases its uptake of the stains and dyes we use to see it, so it looks darker. It's more complex than that – but that's it in a nutshell.

Do you find other things?

We find a lot of infections that weren't clinically suspected. The cervix is very prone to the fungal infection thrush, for example. And two common viral infections we find are the human papilloma virus (HPV) and the herpes virus. They're too small to see but they have an effect on the cells. HPV

takes over a cell's machinery, and uses it to make its own new DNA. You can see that in the size and shape changes in the nucleus.

How do you become a cytologist?

I did a degree in biomedical science and gradually moved up through the ranks to become a consultant. Cytology isn't the easiest of healthcare disciplines to learn. You have to develop the visual skills to recognise cancer, and that takes a lot of practice. So there's a two-year training programme. You have to work in a cytology lab and screen a minimum of 5000 cervical smears, then pass a rigorous exam. After that you're certified to sign out cervical specimens. It takes several more years of practice to become proficient at reporting non-cervical specimens. You can also enter the profession with four GCSEs. You do the same two years' training, screen 5000 samples and take the exam. But that can limit your career as you can only screen cervical samples.

What qualities do you need?

Your eyesight must be good or possible to correct with spectacles, and you must have passed a recent standard eye test. You also need to be able to sit still and concentrate for long periods. It's meticulous work. And you must be able to make sound judgements about whether a sample is abnormal.

Has the technology changed?

Unlike other areas of biomedicine, such as haematology and biochemistry, cytology hasn't been automated. There's no machine that can adequately take the place of the human eye.

Extra online resources



Get online for even more cell-related material from the *Big Picture* team.

Go to www.wellcome.ac.uk/bigpicture/cell to find more articles, videos, image galleries and lesson plans around the cell. This issue's resources include:

- an animation and lesson plan on hearing
- a guide to the evolution of cells
- the story of Henrietta Lacks and HeLa cells
- a video on working with cells in the lab
- image galleries on cell division, cell types and the history of cell imaging.

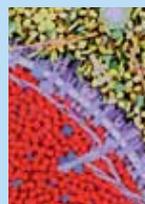
Free science videos and films

The Wellcome Trust, the charity behind *Big Picture*, has a YouTube channel packed with videos on the research it supports. Free to use and share, the videos cover many different areas of biomedical science, from appetite to MRI, Parkinson's disease to chronic pain. Many include interviews with people researching and living with these issues. www.youtube.com/wellcometrust

The Wellcome Film YouTube channel is home to hours of archived medical film, free to use. Browse the channel for all kinds of films, from brain surgery to UK public information films on smoking. www.youtube.com/wellcomefilm

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About the cover

The cover image is 'Blood' (© David S Goodsell, 2000) by David Goodsell, an Associate Professor at the Scripps Research Institute, USA. This illustration shows a cross-section through the blood, with blood serum in the upper half and a red blood cell below. There are Y-shaped antibodies, long, thin fibrinogen molecules (in light red) and many small albumin proteins in the serum. The large UFO-shaped object is a low-density lipoprotein and the six-armed protein is complement C1. The cell wall, in purple, is braced on the inner surface by long spectrin chains connected at one end to a small segment of actin filament.

mgl.scripps.edu/people/goodsell/illustration/public

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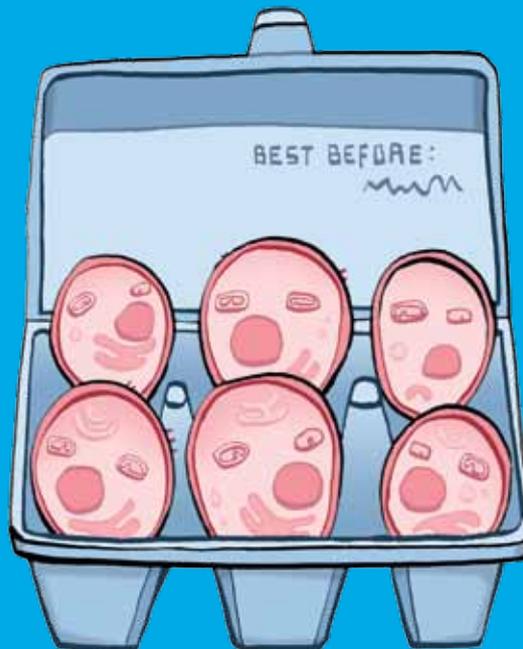
THE CELL

- What are cells for?
- How do cells divide, develop and communicate?
- What are stem cells and why are they important?
- What happens when cells die?

We all share something amazing in common – that we developed from a single sperm and egg to become complicated, sophisticated organisms made of trillions of cells. But how can cells grow and develop to form such complex creatures? In this issue of *Big Picture*, we explore the secrets of the cell – looking at both what scientists understand so far, as well as what's still to be uncovered in this area.

Join us as we take a close-up look at animal cells and get to grips with how

these cells develop, grow and specialise to produce a vast array of tissues and organs with distinct structures and roles. Explore how cells communicate with each other and their surroundings to keep everything in working order, and what happens when these processes goes wrong. Find out what happens when cells die, and when they become immortal. Finally, we ask if stem cells might really hold the secret to treating and curing many diseases, and – if so – at what cost?



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