

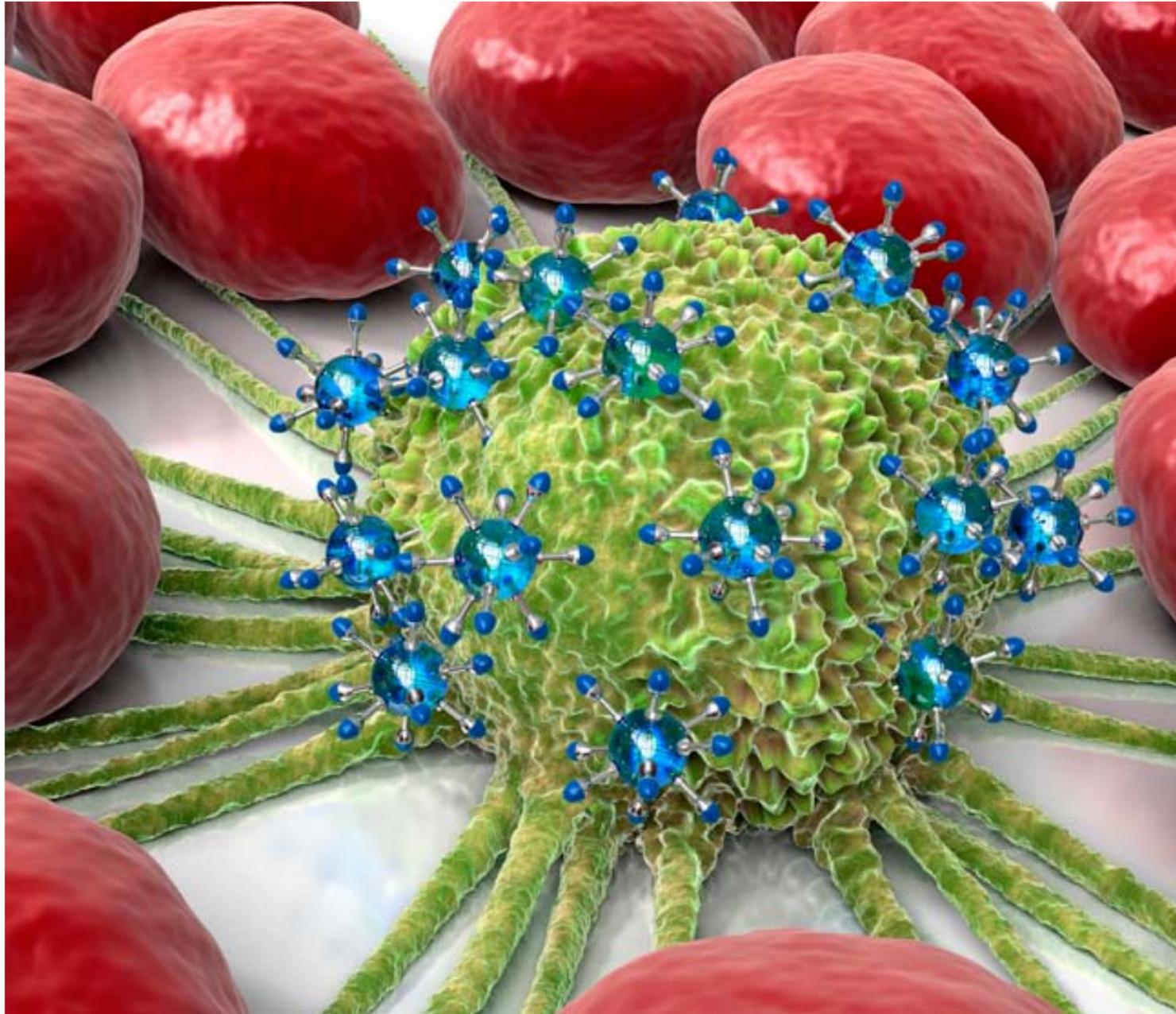
# Nanomedicine

## Science that is changing our lives



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29.04.13 | The Guardian | How nanotechnology can improve our health | guardian.co.uk/nanopinion



An artwork showing medical nanorobots attacking a cancerous cell (in green) while ignoring normal cells (in red)

## Small science, big future

Nanomedicines are revolutionising healthcare – they could end the need for surgery and chemotherapy and ultimately work as medical ‘nanorobots’ in the body. **Holly Cave** reports

**G**ood things come in small packages, or so they say. But there’s small, and then there’s nano – things so tiny that they are almost impossible to imagine. A nanometre is just a billionth of a metre wide. It’s the length your fingernail grows in a second; a sheet of paper is 100,000 nanometres thick. And yet we’re rapidly learning more and more about how to create and manipulate these really small packages – and the resulting nanomedicines could become a vital weapon in our arsenal to combat a huge range of diseases.

“There’s no doubt that we need improved treatments for a wide variety of diseases, ranging from cancer to tuberculosis,” says Vicki Stone, director of Nano-Safety at Heriot-Watt University. “Nanomedicine offers lots of exciting opportunities to improve diagnosis, targeting and treatment of these diseases.”

Sometimes, however, molecular engineers just like to show off. In 2011, IBM created the smallest ever three-dimensional map of Earth, featuring a replica of the Matterhorn measuring just 25 nanometres high.

### Part of everyday life

Nanotechnology is already a reality in many areas of our lives – from the food we eat to the cosmetics we rub into our skin – and, while development is slower, medicine is no exception. There are approved

nanomedicines that treat certain types of cancer, high cholesterol, fungal infections, hepatitis and more. Nanoparticles and nanomedicines – and one day, perhaps even nanorobots – could be used not just for treatment and drug delivery, but for vaccinations, imaging the body, spotting infections, and engineering new tissue.

We could tackle disease on the same scale at which it occurs, says chemist and Nobel laureate Richard Smalley: “Human health has always been determined on the nanometre scale; this is where the structure and properties of the machines of life work in every one of the cells in every living thing. The practical impact of nanoscience on human health will be huge.”

Take cancer, which the vast majority of nanomedicines in development are designed to treat. Almost two decades ago, the chemotherapy medication Doxil was approved for treating Kaposi’s sarcoma – a rare cancer often found in people with AIDS – and it is now also used to treat some other cancers. Doxil uses nanotechnology knowhow to carry the drug doxorubicin to the cancer cell, encapsulating it inside globules of fat (liposomes) about 100 nanometres wide. This nanoformulation, and others like it in development, may not only better target the drug to the tumour, but could reduce unpleasant and destructive side-effects such as bone marrow breakdown and damage to heart muscle.

Conventional methods of cancer diagnosis – typically biopsy and surgery – are

invasive and often come too late, while treatment with chemotherapy is a scatter-gun approach – dousing the whole body with toxic chemicals without directly targeting the tumour. Nanoparticles have the potential to change this by offering earlier, non-invasive diagnosis and more targeted treatments that avoid side-effects. Their size helps. Nanoparticles can be selected by size and fine-tuned to slip easily into the unusually leaky blood vessels of tumours. A peculiar effect they have – known as the enhanced permeability and retention (EPR) effect – is to then remain there, accumulating where they are most needed.

### Start from scratch

But it’s not just about being tiny. Nanomedicines can be engineered from scratch, piecing together particles to create multifunctional complexes. This means that nanomedicines would be tailored to target a certain part of the body. They could be made magnetic or responsive to light so that they could be activated by a remote trigger. They could even carry both drugs

**‘We’ll be able to place the component parts of human cells exactly where they should be, and restructure them’**

and tags which would show up in scans – offering imaging and treatment from a single injection.

The ultimate aim of all medicine is to make it smarter and more responsive to real-time changes in the human body. “Doctors still chiefly rely on the body’s ability to repair itself,” says Robert A Freitas Jr, senior research fellow at the Institute for Molecular Manufacturing in California. “But in the future we’ll develop tools for working at the molecular level; precisely and with three-dimensional control. With these tools we’ll be able to place the component parts of human cells exactly where they should be, and restructure them as they should be, to ensure a healthy state.”

Nanomedicines are blurring the lines between drugs and devices. It may only be a matter of time before we start calling nanomedicines “smart” – in recognition of their potential to respond in real time to changes in the body, acting like a tiny computer to fix problems and possibly even manufacture drugs where they are needed. Some researchers, including Freitas, believe that as they hone their skills of manufacturing precise, nano-sized structures right down to the level of individual atoms, it will become possible to create molecular machines – medical nanorobots the size of a virus or bacteria. Flip to the back page of this supplement to get a glimpse into Freitas’ vision for medical nanorobots. Could this be the future of medicine?

### Introduction

#### Medicine’s future?

In the film *Fantastic Voyage*, a tiny submarine crew navigated through the blood vessels of the human body. And any child of the eighties will remember sci-fi comedy *Innerspace* – the 1987 film it inspired. The same decade saw scientists start using the word “nanotechnology”. Ideas got bigger ... and a lot smaller.

For the most part, nanorobots – or nanobots – still exist only in our imaginations. But there’s nothing make-believe about nanotechnology – creating and finding uses for tiny particles 1-100 billionths of a metre wide. Naturally occurring nanoparticles are scattered through sea spray and rise in the ash spewed out from volcanoes. And by burning wood, we were artificially creating nanoparticles long before we had a name for them.

As you’ll see in this supplement, nanomedicine is a rapidly expanding science. Nanoparticles and nanobot precursors are making their way into cells, into animals, and into us. Nanomedicines could, for example, provide earlier and more accurate diagnosis and offer better techniques for imaging the inside of the body. They are already being used to treat disease. In research labs around the globe, nanoparticles are starting to make the transition from inert treatment to smart device. Science fiction can become a reality.

This supplement is part of a broader consultation process about nanotechnology, organised by the European Commission, which is taking place across Europe until the end of 2015. This consultation includes a series of public meetings, school activities and other events that will gather citizens’ views about the future development of nanotechnology.

Find out more at our dedicated website [guardian.co.uk/nanopinion](http://guardian.co.uk/nanopinion), where you can learn more about nanomedicine and have your say on the key issues surrounding nanotechnology.

**Holly Cave**

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How far can nanomedicine go? We look at the possibility of having nanorobots in the body that “eat” bacteria and viruses

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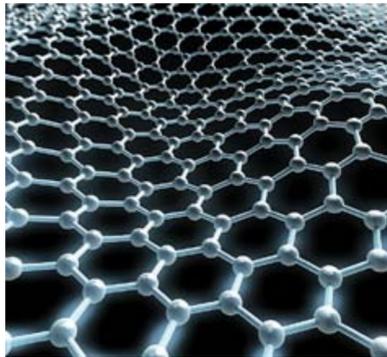
Nanopinion is an EU-funded project gathering a consortium of education and media professionals aiming to communicate, dialogue, and engage with the European public in issues of nanopinion. Through a series of pan-European campaigns and events for a variety of sectors, the project partners hope to take a vital step towards building a public consensus in nanopinion issues.

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**DIAGNOSING DISEASE**

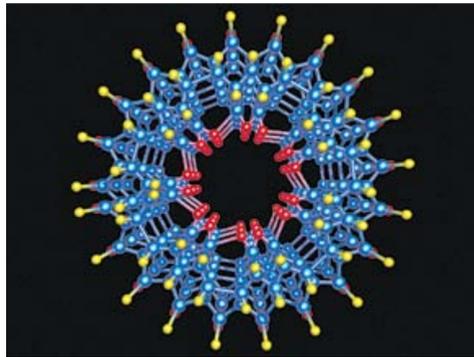
Young Hee Lee and his team at Sungkyunkwan University, South Korea, are using nanotechnology to detect signs of Parkinson's disease. Parkinson's patients have 25% less uric acid in their blood than normal, and spotting that early would be a major help in diagnosing and treating the disease. But it is fiddly to measure the small differences in uric acid concentration with simple, cheap devices. Cuning use of nanotech changes everything. Lee's team used super-holey sponge made from graphene (right) - single atom-thick layers of carbon that conduct electricity really well. Inside the sponge's pores, Lee grew nano-sized needles of zinc oxide. When wired up to make



an electronic circuit, uric acid molecules in the blood sample stick to the surface of these nanoneedles and lose some of their electrons. The graphene sponge sensor is able to spot tiny changes in uric acid concentration because of the sheer number of zinc oxide needles crammed inside it. And as the needles are nano-sized, they have a huge surface area for the uric acid molecules to stick to. The change in uric acid concentration is worked out by measuring the current produced by the electrons - more molecules means more electrons flow and a larger current. Lee hopes to do more trials. Then, a diagnostic nanotech revolution might get going. **Katharine Sanderson**

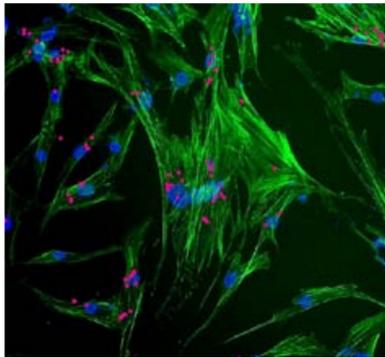
**INTERCEPTING INFECTIONS**

Elderly people often have to undergo surgery to replace their old hip joints with shiny new titanium ones. Unfortunately, these hip implants are not as good as they could be - an estimated 15% of hip replacement surgeries in the USA were for already replaced hips. Thomas Webster of Northeastern University is working on a nano-sized solution, developing a system that will sense problems with the implant and release drugs directly into the implant site. If an infection occurs, the sensor - made of carbon and titanium nanotubes (right) - would detect the bacteria. The sensor would then relay this information through electrical signals to another part of the implant where antibiotics are stored, releasing



**TRACKING TREATMENT**

Little is known about how stem cells behave once they are inside the body, but doctors have discovered that nanoparticles might be an unexpected ally. Stem cells extracted from human fat can help repair a knee affected by rheumatoid arthritis, by suppressing the immune system around the affected areas and helping the damaged tissue to regenerate. But, it's important the stem cells are activated deep inside the joint's tissues. By tagging the cells with magnetic nanoparticles, their path through the body can be tracked, using magnets to steer them, keep them in position, and even activate them. Alicia El Haj, a professor of regenerative medicine at Keele University, has



**BUILDING A NANOROBOT**

The scale of nanotechnology devices is spookily similar to the size of many proteins and cells. If nanotechnologists could make animated robot-like things, in theory these "robots" (the one below is shown on the head of a pin) would be the right size to wander around the body delivering drugs, patching up diseased cells, or killing off cancerous cells. This sounds very sci-fi, but steps towards a nanorobot - albeit nanosteps - are being made.

For starters, to get from A to B, a transport system is needed. How about a nanocar? Chemist James Tour at Rice University in Houston has made molecules that look like cars, with fully functioning wheels made from large carbon-based spherical molecules called fullerenes. Researchers at Oxford University, led by physicist Andrew Turberfield, have made a nanotrail, using tricks borrowed from nature. The team made a track from micrometre-sized tubes that a motor protein called kinesin travels along. The kinesin is adapted to include specific DNA sequences which contain the instructions for the protein to build more track, or to carry a cargo of dye molecules along those tracks.

Once you've made a nanomachine with moving parts, it needs power to become autonomous. Chemist Tom Mallouk and his team at Pennsylvania State University have found a way to make simple nanomotors that move using sound waves. The motors are rods made from gold and platinum. One end of the rod is concave and the other convex, and so ultrasonic waves bounce off each end differently. This gives the rods enough power to spin around and move up to 100 times their own body length per second in water. The machinery for nanorobots to do specific tasks is already under development. Gang Bao at Georgia Institute of Technology makes nanoscale DNA repair-bots, which snip out damaged sections of DNA and using a template, replace them with undamaged segments. Bao's work is aimed at repairing the damaged DNA of sickle-cell patients.

The huge next step is to bring these parts together into a fully functioning medical nanorobot. How likely that is depends on whom you ask. Turberfield says that while medicine is an exciting application, he cannot yet speculate about what his nanorobot might be able to do. Similarly, while Mallouk has tested his motors in live cells - where they can stir up the contents of a cell or punch through its membrane - they do not yet have a medical function. Kostas Kostarelos, a nanotechnologist at Manchester University, is making magnetic swimming nanoparticles that could be guided to a specific place in the body. Yet he thinks that the development of "smart" medical nanorobots is unlikely. More realistic is making a nanomachine capable of repeating the same task over and over, he says. But Mallouk thinks his motors could be developed to power slightly larger robot-like machines that might one day be capable of tasks such as minimally invasive surgery. "We'd like to build in power, logic, control, sensing, communication with other robots, and communication with the world outside," he says.



# What on earth is this thing and how exactly can it help me?

From Parkinson's to hip replacements, we get to grips with some examples of the ways in which nanomedicine could help study, diagnose and treat a range of diseases and medical issues

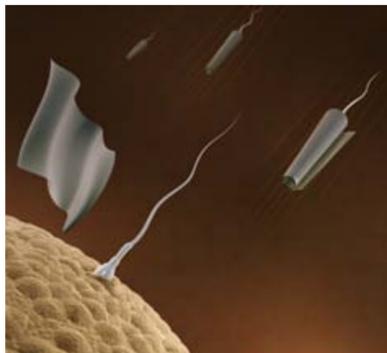
**DELIVERING DRUGS**

Drugs that work well on a petri dish full of cells don't always work well in patients. In the blood, drugs can be recognised as "foreign" and attacked by the immune system. Some drugs are stable in the blood, but do not get into the right kind of cells in sufficient quantity. Others get into the wrong kind of cells, causing side-effects in non-target tissues. Linking or coating these drugs with nanoparticles can help with many of these problems. For example paclitaxel - a chemotherapy used to treat pancreatic, breast, and certain types of lung cancer - works much better when attached to nanoparticles, and this nanomedicine is now in clinical use. Some cancers are particularly hard to get at. Most chemotherapies, for example, do not work very well to treat brain tumours because they are usually injected or ingested, and the blood-brain barrier prevents them from reaching the brain. But a team at Northwestern University in Chicago, led by Alexander Stegh and Chad Mirkin, has come up with a nanoparticle, called spherical nucleic acid (SNA, shown right). "SNAs are able to transverse the blood-brain barrier, accumulate effectively [in brain tumours] upon administration through the bloodstream, and reduce tumour burden without adverse side-effects," Stegh says.

He's tested them in animal models with a type of aggressive brain tumour called glioblastoma and plans to try them in humans very soon. Most of the time, our bodies detect mutation-containing cells that could eventually become cancerous and eliminate them. But tumours can develop if these cells refuse to die. Stegh and Mirkin's solution uses special molecules - small interfering ribonucleic acids (RNAs) - to disrupt the abnormal anti-death signals inside the cancerous cells and cause their destruction. A gold nanoparticle core acts as the lorry, presenting the RNA to the cancer cells in such a way that the whole nanoparticle is engulfed. Once inside the cell, the RNA gets to work. Nanochemotherapeutics are kind of like Choose Your Own Adventure books - many different molecules can be cobbled together to tailor-make a drug. Gold is often the vehicle. It can be covered with drugs specific to the type of tumour and its specific mutations. What's more, it can also be covered with molecules that target the drugs to the right cell and molecules that hide the nanoparticle from our immune system so it cannot be destroyed before it does its job. It is likely this innovation will be an integral part of the upcoming era of personalised medicine. **Megan Cully**

**CONTROLLING CELLS**

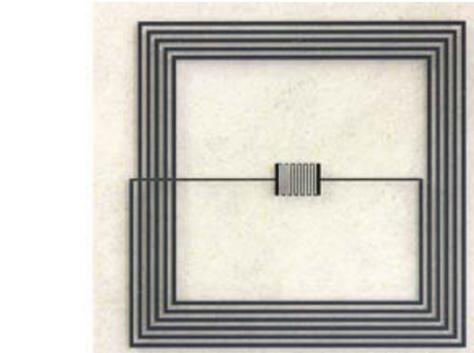
Mix tiny metallic tubes through bull sperm, and you will get a swarm of "spermbots" that can be guided towards an egg (right) using a magnetic field. Scientists at the Institute for Integrative Nanosciences, in Dresden, Germany, suggest that these spermbots could be used for fertility treatment, directing sperm to the egg during IVF. They could also be adapted to carry small doses of drugs to specific targets in the body. The researchers first manufactured films from iron and titanium nanoparticles. By rolling these sheets, they created tubular structures comparable in size to a single bull sperm. When these microtubes are mixed into bull's



**DISAPPEARING DEVICES**

A tiny chip (right) is injected in a wound at risk of infection; it releases heat to kill harmful bacteria, and then disappears. Physical chemist John Rogers of the University of Illinois at Urbana Champaign has successfully tested a device inspired by this idea in rodents. "It is an example of what we call electroceuticals - small electronic implants that perform a medical function in the body under the remote control of radio signals," he explains. Rogers' devices have the advantage that they dissolve after performing their function. Rogers is also working at loading his chip with antibiotics that could be released in response to a wireless trigger. Further applications scientists are working

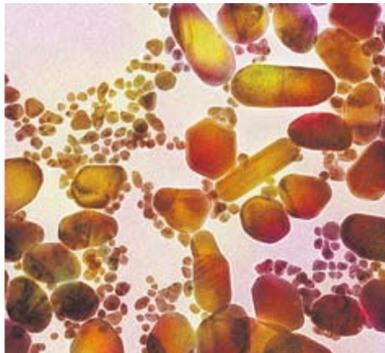
on include LEDs that can be injected into the brain to control neurons with light, or devices to stimulate nerve and bone growth. The key feature of the technology is that it is "transient", that is, dissolvable. This is achieved by manufacturing standard electronic materials just tens or hundreds of nanometres thick - thousands of times smaller than the width of a human hair. "Silicon wears away naturally, but in large circuits you don't notice it," says Rogers. "However, a silicon nanolayer loses 1 to 3 nanometres per day, which means it can disappear in just a few weeks." What remains is silicic acid, something that is found naturally in bodily fluids. **Michele Catanzaro**



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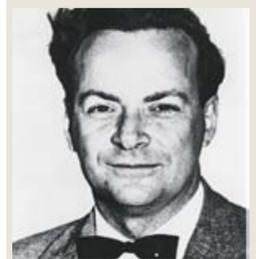
**VISUALISING VIRUSES**

The word "coxsackievirus" may make you giggle, but its effects probably wouldn't. This virus can cause inflammation of the heart, pancreas, or brain and spinal cord (a condition known as meningitis). Relatively little is known about how this virus gets into our cells, but a new nanotechnology tool developed by Hannu Häkkinen's lab at the University of Jyväskylä in Finland could help. It's tough to keep an eye on things as small as viruses, so it's hard to understand how they enter cells to wreak havoc. Häkkinen and his team used gold nanoparticles (right) to coat viruses, tightly attaching the gold molecules to proteins on their surface. Importantly, these nano-modifications did not affect the ability of the virus to infect and kill cells. Instead the tagged viruses provide an accurate picture of what's happening. These golden viruses can be used to take informative, high-resolution snapshots under an electron microscope of viruses attaching to cells, getting inside, and removing their protein coat before replicating. "This has been a cross-disciplinary effort involving chemists, physicists and virus biologists and we are still at the beginning," says Häkkinen. Ultimately, it is hoped the nanoparticles could be used like golden Trojan horses, to deliver drugs to cells infected with these kinds of viruses. **Megan Cully**



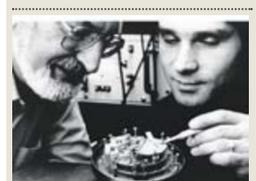
**Nanomedicine timeline**

Conceived nearly 60 years ago, nanotechnology is the science of materials measured in nanometres - a unit so tiny that 80,000 would fit across a human hair. In the last few decades, researchers have begun using nanomedicine to deal with disease.

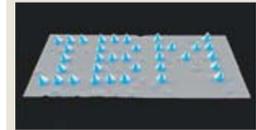


**1959:** US physicist Richard Feynman (above) and mathematician Albert Hibbs predict that tiny machines built from individual atoms could one day be used for healthcare

**1974:** Japanese engineer Norio Taniguchi first uses the word "nanotechnology"



**1981:** The scanning tunnelling microscope (above) makes it possible to see and manipulate nanoscale materials



**1989:** IBM engineers spell out the company's name using 35 xenon atoms

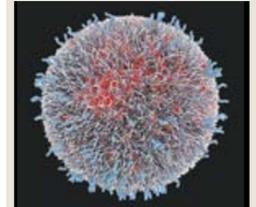


**1991:** Japanese physicist Sumio Iijima (above) is credited with discovering carbon nanotubes



**1995:** Doxil becomes first nanomedicine approved by the FDA to treat AIDS-related cancer, Kaposi's sarcoma

**2011:** Andrew Turberfield develops a "molecular robot", made from DNA and programmed to walk in any direction



**2012:** The first targeted nanomedicine, BIND-014, enters clinical trials

**2030-40:** Nanorobots will protect the human body from disease (as predicted by Google's director of engineering, Ray Kurzweil)

# What are the risks of nanotech?

The licensing of nanomedicines, especially those that contain metals such as iron, is critical - and will need a different approach than conventional medicines



**Vicki Stone and Helinor Johnston**  
Comment

Medical intervention usually involves risk - you only have to look on the leaflet listing potential side-effects inside any pill packet. For all new treatments, the big decision to be made is whether the benefits (cure) outweigh the risks (side-effects, toxicity). We're relatively well versed in predicting and testing how drugs behave in the body, but nanomedicines come with an added level of complexity.

Why? Because the ways in which nanomedicines enter cells and spread around the body are different to drugs, and

their tiny size means detection is tricky. Medical researchers are making use of the ability of nanomedicines to permeate blood vessel walls to improve drug delivery to a specific target.

However, the immune system, which is particularly adept at recognising and taking up bacteria and viruses - also accumulates large amounts of nanomedicine particles. This leads either to the death of immune cells or their activation (resulting in inflammation), and the desired target is unlikely to receive enough of the nanomedicine for it to be effective. Thankfully, scientists are getting better at manipulating the behaviour of nanomedicines in the body in order to overcome these problems.

#### Inflammation concerns

Nanoparticles can have properties which are strikingly different to larger particles of the same substance. A common one - higher surface reactivity - can be hugely beneficial when trying to increase the effectiveness of a treatment - to reduce toxicity, cost and the dose required. But this surface reactivity may come at a price. As mentioned above, the cells of the immune system avidly gather up foreign particles, leading to inflammation. If brief and controlled in size, inflammation is



important for removing foreign particles from the body - indeed, without it the body could not defend itself against infection or pollutant particles. But many diseases are driven by inflammation, including asthma, cardiovascular disease, diabetes and cancer. Additional inflammation in such patients could make their symptoms even worse.

Since these groups of patients are key candidates for treatment with nanomedicines, it will be really important to figure out how potential treatments

**'It will be important to figure out how potential treatments might exacerbate an existing condition as well as treat it'**

might exacerbate their existing condition as well as treat it. Getting the right balance will be essential.

The licensing of new drugs and treatments is controlled by regulatory bodies who work with drug companies to consider safety issues, including inflammation. Yet the majority of this work is carried out in healthy volunteers, with little consideration of how the medicine and the disease might interact inside a patient's body.

This means we'll need a shift in thinking for developing new nanomedicines. The chemistry and physical properties of different nanomedicines vary hugely, so this scenario will not be relevant for all of them. "Soft" nanomedicines that are easily broken down - for example nano-sized fat droplets surrounding and carrying drugs - are likely to break down quickly enough to avoid causing inflammation.

**Researchers at the Welsh School of Pharmacy at Cardiff University are investigating using nano-scale technology to tackle breast cancer cells**

In contrast, imaging contrast agents (used predominantly for diagnosis), which include metals such as iron, are likely to be more persistent in the body, requiring greater consideration of their impacts on inflammation as well as their long-term effects on patients.

There's no doubt we need new medicines - including nanomedicines - for a range of diseases. But considerations of their risks will be essential, and will need a change of approach to that used for traditional medicines.

*Vicki Stone and Helinor Johnston, director and deputy director of nano-safety at Heriot-Watt University*

## The life-saving future of medicine

Nanorobots that 'eat' harmful bacteria, viruses and fungi in the blood or replace the chromosomes from diseased cells with a new sets made outside the patient's body - what are the limits to nanomedicine?



**Robert A Freitas Jr**  
Comment

Medical nanorobots will be the size of bacteria, composed of thousands of molecule-sized mechanical parts perhaps resembling gears, bearings and ratchets. They may be composed of a strong, diamond-like material. A nanorobot will need motors to make things move, and manipulator arms or mechanical legs. It will need a power supply, sensors to guide it, and an onboard computer to control its behaviour. But unlike a regular robot, a nanorobot will be smaller than our red blood cells and able to squeeze through our body's narrowest capillaries.

What will they do? A "microbivore" nanorobot, for example, could act as an artificial white cell, seeking out and digesting germs - bacteria, viruses, or fungi - in the blood. A patient might be injected with a dose of about 100bn of these microbivores. A targeted germ would stick to the nanorobot's surface like a fly caught on flypaper. After being gathered into the microbivore's "mouth", the germ would be minced up

and digested into harmless molecules in just minutes.

A complete treatment of this kind might take just a few hours - far faster than the days or weeks often needed for antibiotics to work - and no bacteria would have time to evolve resistance to these machines as they can to antibiotics. When the nanorobotic treatment is finished, the doctor might broadcast an ultrasound signal to direct the nanorobots to the kidneys where they would be painlessly passed out in the urine.

Similar nanorobots could be programmed to quickly recognise and digest even the tiniest clusters of young cancer cells, long before they spread throughout the body. Cancer would no longer threaten our health.

Medical nanorobots could also perform surgery on individual cells. In one proposed procedure, a surgeon-controlled nanorobot called a "chromalocyte" would extract all the chromosomes from a diseased cell and insert new ones in their place. The new chromosomes would have been manufactured outside the patient's body using a desktop nanofactory. After injection, each nanorobot would travel to its target cell, enter the nucleus and replace the chromosomes, then exit the cell and leave the body. If the patient chooses, inherited defective genes could be replaced with non-defective base-

**'A nanorobot will be smaller than our red blood cells and able to squeeze through our body's narrowest capillaries'**



A vision of the future - nanorobots get to grips with red and white (in yellow) blood cells

pair sequences, permanently curing any genetic disease and even permitting cancerous cells to be reprogrammed to a healthy state.

Perhaps, most importantly, chromosome replacement therapy could correct the accumulating genetic damage and mutations that lead to ageing in every one of our cells. This is the key component of a cure for ageing.

Right now, medical nanorobots are mostly just theory. To actually build them, we need to create a new technology called molecular manufacturing: the production of complex atomically precise structures using positionally controlled fabrication and assembly of nanoparticles inside a nanofactory, much like cars are manufactured on an assembly line.

The first experimental proof that individual atoms could be manipulated was obtained by IBM scientists back in 1989 when they used an electron microscope to position 35 xenon atoms to spell out the three letters of the company's logo. Similarly, inside the nanofactory of the future, carbon-rich feedstock molecules such as natural gas, propane, or acetylene will be manipulated by massive, parallel arrays of tiny probes to build the atomically precise diamond-like machine parts needed to assemble medical nanorobots.

The Nanofactory Collaboration, a loose-knit community of scientists founded in 2000, is co-ordinating a research and development programme to design and build the first working nanofactory that could create medical nanorobots ... hopefully within the next 20 years.

*Robert A Freitas Jr is a senior research fellow at the Institute for Molecular Manufacturing*