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Medical research

The resources of the infinitely SMALL

Editorial

Industrial research: the European blockage

The European Commission has just published its annual scoreboard of industrial investment in R&D. On close analysis of the figures, an intriguing if not altogether rosy picture emerges. It would appear, for example, that the 700 EU companies most active on the R&D front invested €102 billion in 2004, which is half that of the top 700 – for the most part American – non-European R&D investors. At the same time, the major European companies have no cause to envy their US counterparts: the research top 50 includes 18 EU companies, 17 American and 12 Japanese. Also, the world number corporate R&D investor is a European company, DaimlerChrysler, with an investment of €5.7 billion in 2004 (even if the detractors insist that it is essentially a bi-national company). This ranking is also a reminder that the automotive industry is the number one R&D investor, accounting for five of the top ten companies. Ensuring the safety and comfort of our car journeys absorbs about 10% of the global research potential.

The European weaknesses are both structural and cultural. EU companies are less present in the research-intensive sectors, in particular the information and communication technologies (except for world leader Nokia). What is more, European companies invest on average much less in research than their foreign cousins: 2.9% of turnover compared with 4.2%. It is no doubt a question of commitment and confidence in the future. But most worrying of all is that the gap between Europe and the rest of the world is continuing to widen. Over the past three years, R&D investments by the top 700 European companies have grown by just 0.1%, compared with 4% for the top 700 non-European companies. The EU's industrial investments in R&D are thus insufficient to boost growth and, given the low expected increase in GDP, such growth will be insufficient to have an upward effect on investments in R&D. Breaking this vicious circle remains a major challenge that is more urgent than ever for Europe.

http://eu-iriscoreboard.jrc.es/index.htm

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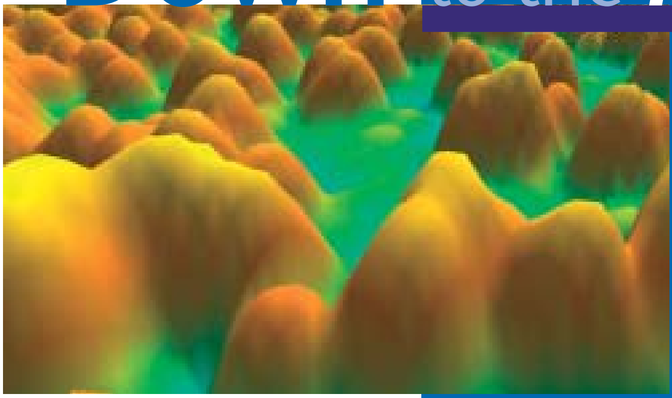
Down to the *nearest billionth*



Membrane proteins, imaged by scanning force microscopy.

"There is plenty of room at the bottom," the US physicist and 1965 Nobel prizewinner Richard Feynman declared back in 1959. This witticism was his way of saying that there was nothing – save for the lack of suitable tools – to prevent scientists one day from working directly on the atomic scale. The world would then witness a revolution, with researchers breaking free of the confines of conventional physics to enter a universe governed by the rules of quantum physics. That day has now arrived – over the past decade the 'nano' prefix has been applied to activities in a wide range of fields that involve studies or operations on the atomic scale.

The suitable tools began to appear in the 1980s when a team of researchers in Zurich developed a new family of microscopes(1) enabling them to observe and handle individual atoms. It was not long before these tools spread from the physics laboratories to applications in other fields. Thus, from 1995, the double concept of nanosciences and nanotechnologies emerged progressively – terms coined in reference to the nanometre, a unit of measurement equivalent to one billionth of a metre, or the space occupied by ten atoms of average size.

All the rage

Over the past decade, the 'nano' has been 'all the rage' in the research world, with conferences, journals, seminars and patents all dedicated to the concept. It has also given rise to a growing number of neologisms – nanoparticles, nanomachines, nanomaterials, nanoelectronics, nanochemistry, nanotechnology, nanomedicine, etc. – which refer to activities that involve the study or handling of living or inanimate matter on the atomic scale. These 'nano approaches' are seen as revolutionary in the sciences and technologies whose applications are transforming our everyday lives. "Nanotechnologies hold the promise of stimulating economic growth by creating new products that improve the quality of life in nearly all fields," believes Renzo Tomellini of the Nanosciences and Nanotechnologies Unit at the European Commission's Research Directorate-General(2).

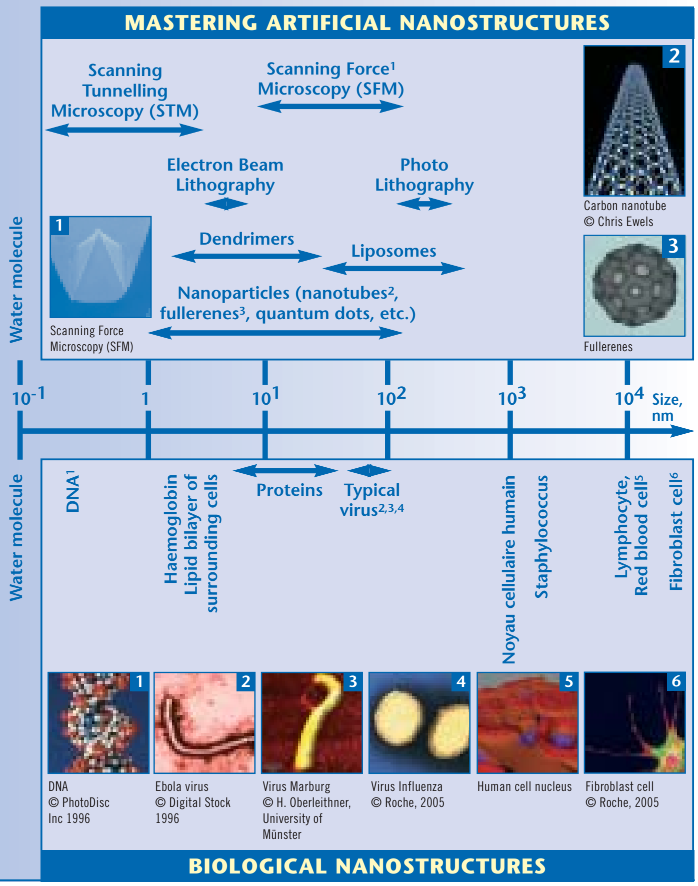
But why does this focus on the nanoworld and its new vocabulary have such particular resonance today? The answer varies depending on the discipline. In the field of physics or chemistry, for example, it is clear that the usual properties of materials, such as their conductivity or fusion point, change when one reaches the nanometric scale, at which point they are governed by the laws of quantum physics. This change of scale also has important practical consequences. Transistors are one example. In a few years' time, their miniaturisation will come up against the physical limit of the size of the silicon atoms, below which it will not be possible to descend. Electronics will therefore have to be rethought in quantum terms, thereby opening up a whole new field of research. Another example is chemistry, or materials science, where nanotechnologies have opened up exciting new prospects for designing new forms of matter by assembling molecules one by one.

Enthusiasm and prudence in biology

In the field of biology, opinions are divided. "Yes," asserts Kees Eijkel of the University of Twente (the Netherlands), "the nano approach is revolutionary because it makes it possible to think of life as a very complex nanotechnological system constructed as a result of a series of self-assembly processes." But Rogério Gaspar, of Coimbra University (Portugal), is more modest in his claims: "Nanotechnologies simply repeat the former approaches on a smaller scale". As to Shimshon Belkin of the Hebrew University of Jerusalem, he cleverly sidesteps without coming down on one side or another: "I studied microbiology at university and I am told that what I am doing now is nanobiology. Does this change of prefix have anything to do with promoting the concept I wonder?"

But there is one point on which the majority of researchers agree and that is the medical benefits that can be expected, whether or not there is any change in the scientific paradigm. Yet here too there remains a certain 'modesty' in the face of some announcements that could ultimately result in disappointments. "By making it possible to bring together what were previously isolated technologies, nanotechnologies promise dramatic progress in the field of the early detection of tumours and cancer treatment," confirms Mauro Ferrari, head of nanotechnologies at the National Cancer Institute (USA), whose aim is to reduce cancer deaths dramatically "by 2015".

(1) Scanning force microscopes and scanning tunnelling microscopes.
(2) All the citations in this dossier were collected at the EuroNanoForum 2005 Conference, held at the beginning of September 2005.



But it should also be remembered that it was President Nixon who announced – back in 1971 – that cancer would be eradicated within 20 years. And the biologists of the 1980s were rather too quick to announce gene therapy by the year 2000, too. This mythical year is now behind us and, although promising, the technique is still at the research stage. "There is widespread confusion between the reality of nanotechnologies (in the short term), their potential (in the medium and long term) and the stuff of science fiction," explains Gian Carlo Delgado Ramos of the Autonomous University of Barcelona, who subtly adds "and no doubt not only on the part of the general public".

Realistic prospects

One can nevertheless venture to make certain predictions as to what the most likely progress in the field of nanomedicine will be – which is precisely the mission of two joint initiatives launched earlier this year with the support of the European Commission.

In September 2005, the new Nanomedicine Technology Platform, an assembly of some 40 experts with their roots in academic or industrial research, presented its Vision Paper for 2020 which sets out the expected changes. The essential basis for its predictions is the belief that, in the future, nanotechnologies will make it possible to "carry out complex repairs at the cell level inside the human body" because "artificial nanostructures have the unique property, due to their size, of being able to interact with biomolecules on the surface of the cell and inside it". As a result, these specialists anticipate developments in three principal fields: diagnostics (including imaging), the targeted and controlled release of medicines in diseased organs and, finally, regenerative medicine.

The year 2005 also saw the third annual EuroNanoForum[3], held in Edinburgh (Scotland) in September, at which these three subjects were central to the debates.

In a context where the economies of the developed countries are all facing growing health expenditure linked to ageing populations, it is not difficult to understand why nanomedicine is viewed as highly significant for public health, a key issue for research policy-makers and a strategic market for the pharmaceutical industry.

To find out more

- **Nanomedicine Technology Platform**
  www.cordis.lu/nanotechnology/nanomedicine.htm
- **EuroNanoForum**
  www.nanoforum.org

(3) See also box *Let's talk nano-society* page 10.

Microchromatographical column.
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Europe as a challenger

In the race to conquer the nanoworld, the United States is a little ahead of the European Union and Asia. A study carried out by the British bureau Marks & Clerk shows that US laboratories and companies account for 40% of patents either issued or applied for in the field of nanotechnologies during the 2002-2005 period. But the study also stresses that "the gap between the United States and Europe, which is much narrower than in other hotly contested fields such as cancer or stem cell research, is rapidly closing".

The firm commitment by the EU's Sixth Framework Programme to financing research in nanotechnologies (€370 million out of total expenditure in Europe of €1.3 billion) has no doubt made a vital contribution to this, in particular by virtue of the emphasis placed on training and the networking of skills. In the field of nanomedicine, Nano2Life is a Network of Excellence bringing together a sector that remains very fragmented, its 23 European members working on health-related applications. "Our ambition is to be an interface between the nano- and biotechnologies, between the public and private sector, and finally between academic, industrial and clinical research," explains network coordinator Patrick Boisseau of the French Atomic Energy Commission.

The European Council and Parliament are currently looking at the Commission proposal to double the financing of nanotechnologies under the Seventh Framework Programme (2007-2013). The race has only just begun.

Despite the very real progress achieved by medicine, researchers and doctors always seem to come up against the same obstacles: illnesses that are diagnosed too late, medicines that are either ineffective or effective but toxic, and the inability to regenerate the organ or tissue damaged by injury or disease. On these three points – and whether in the face of cancers, accident injuries, cardiovascular, neurodegenerative or immune diseases – the 'nano approach' promises crucial breakthroughs.

Treating & healing on three fronts

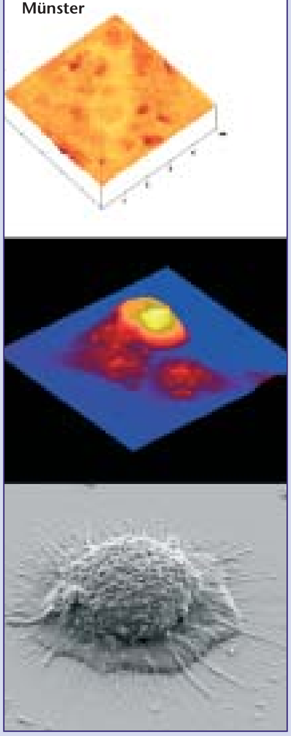
The importance of early diagnosis is well known, especially for cancer. The earlier the disease is identified, the better the chances of combating it with surgery or chemotherapy. But there is a dilemma. While progress in *(in vivo)* imaging and *(in vitro)* biochemical and genetic analysis has considerably improved detection possibilities, the examinations are long, costly and sometimes painful for the patient. So, doctors hesitate to prescribe them. It is by rendering these existing diagnostic methods more rapid, reliable, sensitive and economic that this new approach by nanomedicine can help resolve the dilemma.

In vivo viewing

Real progress has been made in recent years in two fields. The first is *in vivo* diagnostics. Whether it is scanning, magnetic resonance imaging or tomography, all the techniques for viewing the human body require the injection of tracers or contrast agents.

"Conventional contrast agents make it possible to visualise the anatomy, but are not very effective in evaluating the psychological or molecular processes," explains Andreas Briel of the Schering Social Research Centre in Germany. "That is why nanotechnologies are so interesting as they make it possible to assemble an inert marker that can be identified by the imaging device and a biological ligand that is able to recognise a particular organ or cell type. Because of their small size, these markers penetrate the tissue more easily and improve the image resolution."

Novel diagnostic approaches: cell surface characterisation of pancreatic tumour cell lines.
© J. Schnekenburger, Department of Medicine B, University of Münster



On-chip laboratories

The second field is the generalisation of DNA chips. These *in vitro* devices make it possible to analyse the gene expression of a cell in just a few hours by means of oligonucleides fixed to a solid support that activate a light or electrical signal when they recognise the complementary DNA sequence. Unknown just a decade ago, these chips are now widely used in diagnosing gene expression disturbances in the cells of very small samples which conventional methods were unable to analyse – in the case of biopsies on patients suffering from stomach cancer, for example.

The ultimate aim of nanomedicine is to identify the tumoural transformation immediately the very first cell is affected. Although there is still a very long way to go, research is beginning to identify the path. Techniques for a rapid analysis of the proteinic combinations of the

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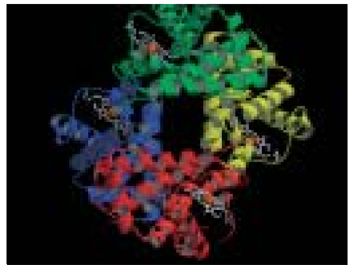

Crystal structure of human deoxyhaemoglobin.
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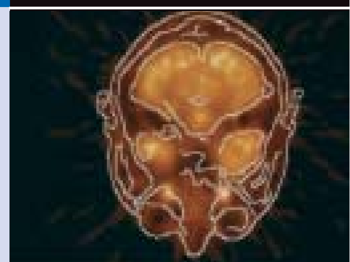
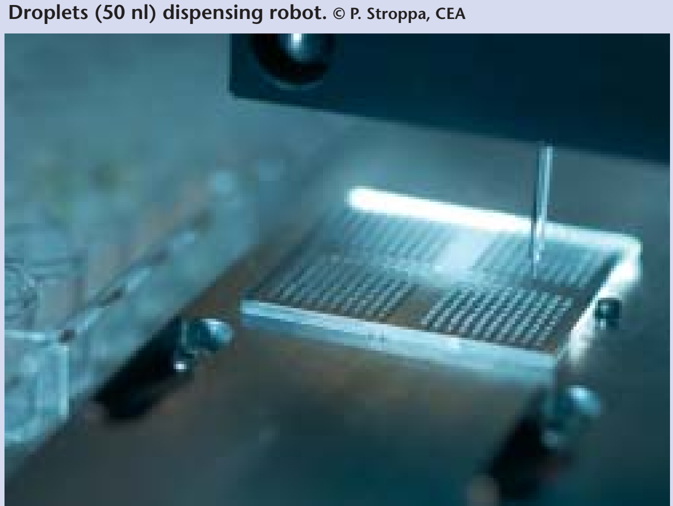


Brain pictures with Positron Emission Tomography (PET) and Nuclear Magnetic Resonance (NMR). © CEA

Fluorescence microscope.
© P. Stroppa/CEA

Droplets (50 nl) dispensing robot. © P. Stroppa, CEA



cell surface – to seek the signature of tumour cells – are at an advanced stage of development. These use protein chips which function on the same principle as DNA chips, but with antibodies that recognise the peptides expressed on the surface of cancerous cells in the place of oligonucleotides.

Gene delivery using ultrasound. The presence of gas in the gene-filled microbubbles allows ultrasound to burst them.
© Unger et al. Therapeutic Applications of Microbubbles

More futuristically, there is also talk today of 'on-chip laboratories'. This expression refers to miniaturised systems that make it possible to carry out, in parallel, in the minute cavities fed by microfluids, several hundred biochemical analyses whose results can be studied in real time. "Although considerable sums have been invested in this field, on-chip laboratories have not been developed very much commercially," says Rutger van Merkerk of Utrecht University, who has just completed a strategic study of the sector's 20 leading players. "It is a promising technology, but one that it is still at an early stage of development and seeking fields of application."

The race for miniaturisation, in fact, poses some serious technical problems. Jeremy Lakey, scientific director of the UK company Orla Protein Technologies, explains: "To make an interface between the biological systems and electronic devices, the latter must be around the same size as the DNA, membranes and proteins, which means we are talking about scales of under 100 nanometres. This implies we must develop nanofabrication methods in the field of electronics."

The delivery headache

After the diagnosis comes the treatment. Except in special cases (see box entitled 'Tumour-killing nanoparticles' p8), the nano approach is unlikely to result in genuinely new treatments. It does, however, hold the promise of a radical improvement on one key point: the delivery of medicines. For a molecule to be effective – whether the result of conventional chemical syntheses or concocted using advanced biotechnologies – it is not enough for it to be able to improve the condition of the sick organ. It must first reach that organ, which is not easy for large molecules such as proteins.

"Proteins are being used increasingly as therapeutic agents for several diseases, including cancer, but their development comes up against the problem of passing through biological membranes, their structural fragility and their rapid breakdown in the human body. As a result, today they usually require parenteral administration, which means complicated and painful injections," stresses Peter Venturini, director of the Slovenian National Institute of Chemistry.

So does that mean the solution lies in using small molecules that can circulate freely in the body? At one point that may have been the view, but "the slow progress in treating diseases such as cancer using molecules with a low molecular weight brought a change of strategy, with the focus now on administering medicines directly into the affected organs", explains Costas Kiparissides of the Aristotle University in Thessaloniki (Greece). Gene therapy, on which so many hopes were pinned in the 1980s, also comes up against this problem of delivering the DNA medicines to the target cells.

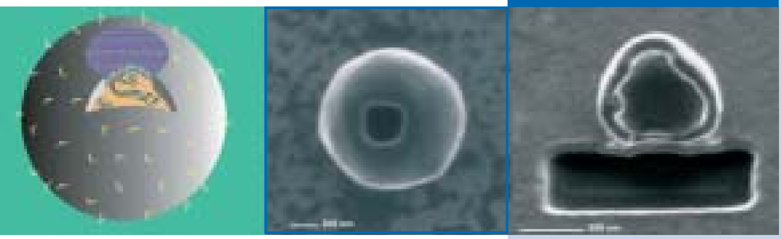
In addition to this scientific question, there are also economic considerations. As Andreas Jordan, doctor and director of the MagForce company, admits, "this research into delivery is also a way of giving a second life to molecules that have entered the public domain, by changing their presentation".

Transport engineering

So how can the nano approach revolutionise the delivery of medicines? The answer lies in a very simple geometric fact: for a given mass, the more a substance is contained in small particles, the greater the total surface area with a biological activity able to interact with the receptors on the cell surface.

This explains the attention focused on reducing the size of the systems envisaged for transporting the medicine to its target organ – for example, in tiny bubbles encapsulating the therapeutic molecule made up of single-layer lipids (micelles) or multi-layer lipids (liposomes), or otherwise coated in biodegradable polymers packed with antibodies able to recognise the target cell. All of which brings us to the realms of the very fine engineering of molecular 'transport' vehicles that must, at the same time, protect the medicines from breakdown.

As Richard Aljones, of Sheffield University, likes to say, "the most wonderful example of nanotechnology that we know is none other than the



FROM LEFT TO RIGHT:
- **Schematic of nanofabricated biomimetic drug-delivery vehicle. The surface of a hollow polystyrene bead containing the desired payload is functionalised for specific targeting. The payload is released through the membrane lipid bilayer covering the hole fabricated in the scaffold.**
- **Transmission electron microscopy image of a hollow polystyrene bead with a nanofabricated hole.**
- **Transmission electron microscopy image of the cross-section of an 'artificial cell'.**

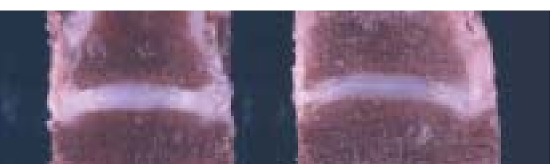
© A. Dudia and V. Subramaniam, University of Twente, The Netherlands

living cell, that constructs itself all alone by a process of self-assembly of its parts". To build these devices, an initial approach therefore is to draw inspiration from the principles at work in living nanometric systems, such as ribosomes or membranous enzymes. Ultimately, it is even envisaged to equip these nanoparticles with remote delivery instructions, so as to trigger the medicine release (by means of electromagnetic waves or infrared stimulation, for example) once the vehicles reach their targets.

The miniaturisation that permits this nano approach also has another advantage in that it makes it possible to envisage innovative ways of administering medicines that are more practical, effective and/or less painful, such as pulmonary administration with nanoparticle sprays or transdermal administration, in particular for unconscious patients.

Autoregeneration

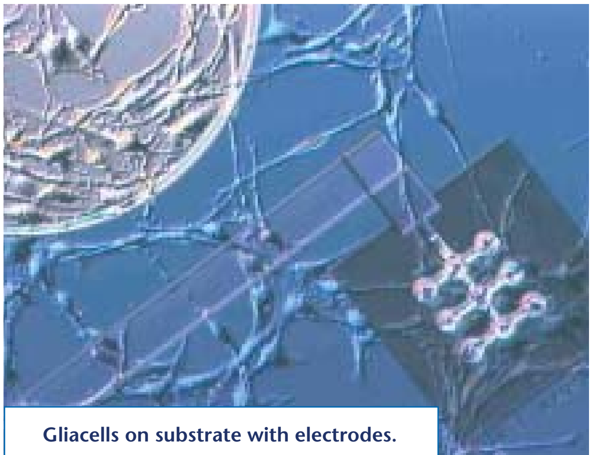
The third and final field of application for nanomedicine is regenerative medicine which aims to help the body heal itself. The first stage was the replacement of defective organs, which appeared in the 1970s when the first materials for implantation in the human body were developed. But these were no more than inert 'spare parts' that were not biodegradable and had also often been developed for quite different applications. In the mid-1980s, a second generation of ceramic- and glass-based materials became available. These were either biodegradable (once the lesion repaired) or able to stimulate autoregeneration action – but never both at the same time. The challenge for today's researchers is to combine these two properties of biodegradability and bioactivity in a single



LEFT: Intervertebral disc, 12 months after treatment with autologous disc chondrocytes.

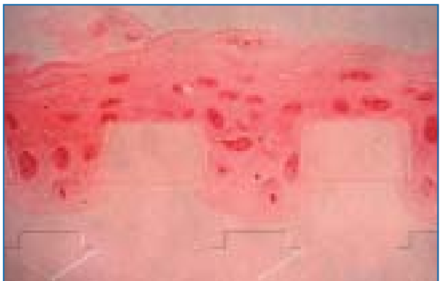
RIGHT: untreated intervertebral disc. Regenerated discs mimic native disc morphology; autologous treatment promotes tissue regeneration.

© T. Ganey, co.don AG



Gliacells on substrate with electrodes.

© Fraunhofer IBMT, St. Ingbert



Engineered epithelium.

© Fidia Advanced Biopolymers

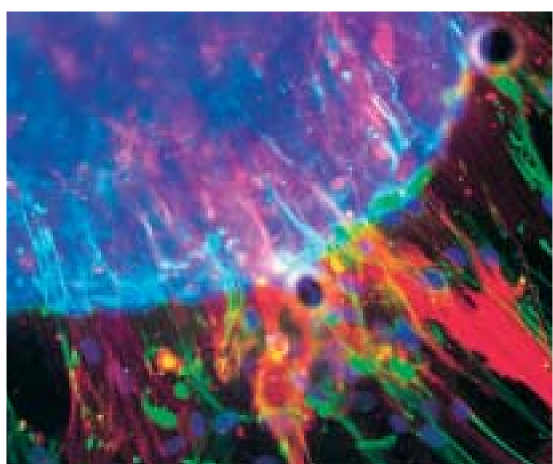
structure. When working on a nanometric scale it is indeed possible to design combinations of inert bodies and biological molecules previously inaccessible to conventional chemistry.

Cellular differentiation, intelligent materials

Another avenue is also opening up for a command of cellular differentiation, at the heart of stem cell research. "In the traditional approach to cell therapy, the cells are grown in a liquid environment, which limits their differentiation possibilities. We are currently seeking to grow them on a solid surface covered on the nanometric scale with combinations of proteins able to induce their transformation into a desired cell type," explains Günter Fuhr of the Fraunhofer Institute for Biological Engineering (St Ingbert, DE) and coordinator of the European project CellPROM (Cell Programming by Nanoscaled Devices).

Finally, as we saw in connection with medicine delivery, the nano approach can permit the design of 'intelligent' materials able to adapt their behaviour to local biological conditions or external stimulations. "Such materials, when used as both a nutritive and structural matrix, could serve to multiply healthy cells so as to then reimplant them in the diseased organ," comments Alessandra Pavesio, of the Italian company Fidia Advanced Polymers, who is working on the application of this principle for meniscus regeneration in the European Meniscus project.

Like many industrialists in this sector, Pavesio wants the European regulations to be made more flexible so as to speed up clinical trials on nanomedicine products. David Rickerby, of the European Commission's Joint Research Centre Institute at Ispra (IT), nevertheless believes that "the present legal framework, which does not differentiate between nanomedicine and conventional products, is sufficiently flexible to integrate innovations of this type at their present stage of development, even if regular evaluation will have to be made to allow for scientific progress". So it seems that the law will not be caught off guard by the expected scientific and technical changes brought by nanomedicine. ■



Spontaneous stem cell differentiation.

© Fraunhofer IBMT, St.Ingbert

Towards artificial corneas?

The cornea that protects the surface of the eye consists of two layers of epithelial cells surrounding a proteinic and cellular matrix (the stroma) of complex structure that is both transparent and very rigid. Corneal lesions are responsible for about 6 million cases of blindness worldwide. Every year in Europe over 27 000 cornea grafts are carried out, but the lack of donors, problems of immunological compatibility, and risk of disease transmission all mean that this method

does not give full satisfaction. Therefore, the ultimate aim of the 14 teams from nine European countries working within the Cornea Engineering consortium is to construct artificial corneas for these ophthalmologic grafts.

Artificial corneas could also serve to test the ophthalmologic toxicity of cosmetics and thus reduce the need for experiments on animals. “The Italian consortium team member has already succeeded in reconstructing the epithelial layer by means of autologous cells grafts. The next step is to reconstruct the stroma. By assembling protein fibres, on the nanometric scale, the aim is to develop a matrix within which the stem cells can be differentiated,” explains David Hulmes, of the Institut de Biologie et de Chimie des Protéines in Lyons (FR), the project coordinator.

Tumour-killing nanoparticles

To find out more
- www.magforce.de

Destroying tumours with heat is not a new idea, but for years it has faced the major obstacle of side effects due to the difficulty of restricting the hyperthermia to the tumour region alone. The Berlin company Magforce, founded in 1997, has now come up with an original solution to the problem. It is based on the injection of iron oxide nanoparticles with a special protein coating that ensures they are only absorbed by the tumour cells which are then unable to excrete them. “Once they penetrate these cells, the nanoparticles act as tiny receiver aerials,” explains Andreas Jordan, the company’s founder. “The application of a magnetic field then creates a local hyperthermia that kills the tumour cells.”

Successful phase 1 human clinical trials have already been carried out using this promising technique. Phase 2 trials, aimed at demonstrating effectiveness in certain cases of prostrate and brain cancer, are currently being carried out at the Charity Hospital in Berlin. In the light of the very encouraging results, MagForce expects this new treatment to be marketed by 2007. Work is already in progress on a new generation of these nanoparticles. When incorporated in proteins that specifically target tumour cells, these can be injected directly into the bloodstream rather than into the tumour, as is the practice today.

TOXICITY under

Technicians and a robot producing oligonucleotides.
© P. Stroppa, CEA

“It is not because of all the current excitement surrounding nanosciences that we are looking at the toxicity of nanoparticles,” stresses Ken Donaldsen, scientific director of Edinburgh University’s Inflammation Research Centre (Scotland). For this toxicologist and pillar of the British Association for Lung Research, there are two main reasons for scientific interest in the risks of exposure to nanoparticles.

The first is awareness of the dangers of transport-related pollution which, according to the WHO, results in 80 000 premature deaths a year in Europe. It is now clear that the pollutants that are usually studied (ozone, nitrogen or sulphur monoxide, etc.) do not in themselves explain this mortality, and that small suspended particles, known as PM10s(1), which are released by diesel engines in particular, also play a role.

The second relates to what was a huge failure on the part of toxicologists in being unable to warn of the health risks of asbestos, as a result of which tens of thousands of people suffered. In this latter case too, it is minute suspended particles, just a few micrometres in length, which are responsible for the damage. The smaller the particles the easier it is for them to penetrate the respiratory system. So, if microparticles such as those linked to air or asbestos pollution present such serious risks to health, there would seem to be good reason to be suspicious of particles that are a thousand times smaller.

Risk = danger x exposure

Toxicologists are not starting from scratch in their exploration of the toxicity of nanoparticles. They already have a conceptual framework summed up by the equation: risk = danger x exposure. The danger is an intrinsic

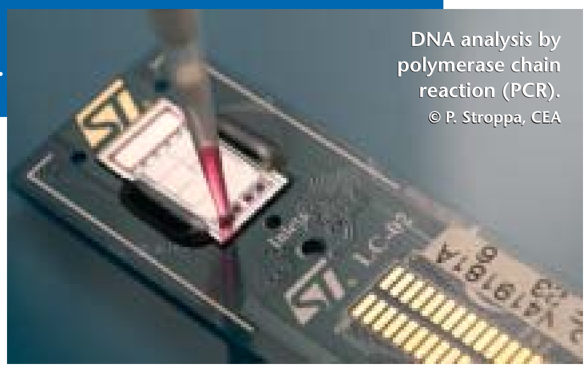
(1) PM10 refers to the fine suspended dust particles of an aerodynamic diameter of under ten micrometres. Formed of both primary and secondary pollutants, of natural or anthropic origin (soot, geological matter, abrasion dust, biological matter, etc.), this dust has a very variable composition (heavy metals, sulphates, nitrates, ammonium, organic carbon, aromatic polycyclic hydrocarbons, dioxins and furans).

nano-surveillance

The 'nano' prefix can cause confusion, insofar as it can relate to the dimension in which a new kind of scientific activity is conducted (nanotechnologies) or the depth of analysis of a phenomenon being studied. Thus, when one speaks of research on the toxicity of nanoparticles, the reference is not to a danger posed by nanotechnologies specifically – although this could be the case – but to the mechanisms at work when one analyses the specific toxic effects of all kinds of particles (of anthropic as well as natural origin) on the nano scale. This is a new field and it is only now being explored.

characteristic of a substance, while the exposure varies depending on behaviour. As Ken Donaldsen explains, "the danger of using a chainsaw is of cutting oneself, but the risk is very different depending on whether it is used by a forester wearing all the protective gear or in a juggling act!".

In practice, it is difficult to quantify these two elements. The danger depends on the nature of the nanoparticle, its size and active surface area, the individual who absorbs it, the organ studied, and often varies depending on whether the exposure is isolated or regular. As to the exposure, that is a factor that has to be reconstructed after the event with all the unknowns that this implies.



DNA analysis by polymerase chain reaction (PCR).
© P. Stroppa, CEA

Effective toxicity

The toxicology of nanoparticles is still largely unknown territory for the good reason that we know next to nothing about the two factors in the risk equation. To measure the danger, one must know what pathology to study: mesothelioma, in the case of asbestos; silicosis, in the case of carbon particles; and asthma, in the case of the famous family of airborne dust particles known as PM10s. But as yet we are unaware of what could be the other pathologies caused by nanoparticles and that – if they exist – would depend on their chemical nature.

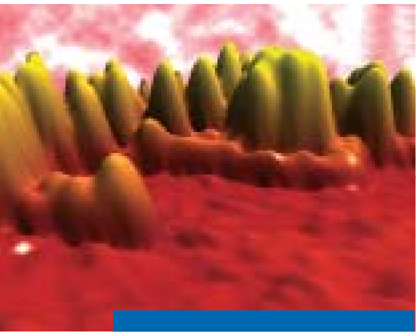
As a result of this inability to evaluate the danger we are unable to estimate the exposure. The latter must be expressed in a unit of measurement that reflects what the specialists call the 'toxicity effect', that is, the principal component of the toxicity. For the PM10s, this is the mass and they are therefore quantified in micrograms/ m^3; for asbestos, it is the fibres, and the unit of measurement is the number of fibres per m^3.

And for nanoparticles? It is impossible to say at present. The only point on which researchers agree is that their surface area must be taken into account. For geometric reasons, 1 000 particles of 100 nanometres in diameter have a bigger surface area than a single particle measuring 1 micrometre in diameter, hence an increase in the possibilities for contact with biological tissue. There is therefore an urgent need to reach a consensus on the unit of measurement because, as Rob Aitken of Edinburgh University's Institute of Occupational Medicine points out, "the rare data we have at present for measuring the toxicity of nanoparticles cannot be compared the one with the other as they are not expressed in the same units".

The safety of nanoapplications

It will not be possible to develop nanotechnologies on an industrial scale without acquiring a better knowledge of the toxicity of nanoparticles, both for industry workers and the consumer. Hence the decision to set up the consortium of 23 academic and industrial laboratories from seven European countries, known as NANOSAFE2. With EU financing of €7 million, the consortium aims to compile a single database of current knowledge of nanoparticles commonly used in industry, such a carbon nanotubes, zinc oxide or silicon crystals. The database will draw on existing knowledge available in the specialist literature but which will now be pooled in a standard format, and the production of new knowledge. On this basis, NANOSAFE2 will study the potential sources of nanoparticles in various industrial sectors (aeronautics, energy, construction, etc.) and what happens to particles when they enter the atmosphere. Resolutely focused on applications, the research should make it possible to improve nanoparticle detection devices and define a scientific basis for rules of health and safety in the workplace.

To find out more
- www.nanosafe.org



Plasma membrane and proteins viewed through a scanning force microscope.
© H. Oberleithner, University of Münster

Ingesting, touching, inhaling

To be able to determine the two key variables of nanoparticles – danger and exposure – toxicologists therefore have no alternative but to return to physiology to determine the path they take in the body. Theoretically, there are three possible means of access to the body's interior and its vital organs: by means of ingestion, through the intestinal mucosa; by means of simple contact, through the skin; or by means of inhalation, with subsequent transport through the blood, through the pulmonary alveoli, or directly into the brain through the neurones and olfactive mucosa.

It is only the latter of these three means of penetration that has so far been confirmed. As Günter Oberdörster, of Rochester University (United States), a pioneer in this field points out, "we have known since 1914 that when administered to a chimpanzee, a poliomitis virus, which measures no more than 30 nanometres, reaches the brain at a speed of 2.4 millimetres an hour by way of the olfactive neurones".

This observation has been repeated on many occasions, to the point of being used as a method for the study of olfactive neurone connections. Oberdöster's work has also shown that nanoparticles could follow this path to quickly reach the upper centres of the brain: the cortex, thalamus and cerebellum. What are the consequences of their presence here? "Our preliminary results, among healthy volunteers, show that inhalation of nanoparticles emitted by the diesel engine changes the electroencephalogram rate," explains Paul Borm of the Centre for Expert Assessment in Life Science in An Herlen (the Netherlands). And in the longer term? "That is one of the questions to be resolved in the coming years, in particular by studying the possibility of neurodegeneration," admits Günter Oderdöster.

Much less is known about the mechanism for absorption by the lungs or intestine. The only certainty here is that exposure to certain nanoparticles can cause cardiac problems in animals. Some believe this is because the cells of the pulmonary epithelium are able to absorb these nanoparticles and transport them to the bloodstream, from where they spread throughout the body and thus also to the heart. Others see it as an indirect effect linked to the inflammation of the pulmonary mucosa through contact with the nanoparticles. Even less is known about possible absorption through the skin. The European NANOderm project was one of the first to tackle this question, through the *in vivo* and *in vitro* study, on human and pig skin cultures, of the passage of titanium oxide nanoparticles through the skin.

This research is not without its economic significance as these particles are widely used in the cosmetic industry and are present in many sun lotions. After two years of research, project coordinator Tilman Butz of Leipzig University (Germany) is reassuring: "Titanium oxide nanoparticles remain blocked in the upper layers of the epidermis and almost never penetrate to the dermis, except along the follicular cells that generate hairs." The NANOderm consortium is nevertheless to continue its research to find out if damaged skin (burns, psoriasis, etc.) continues to act as an effective barrier. ■

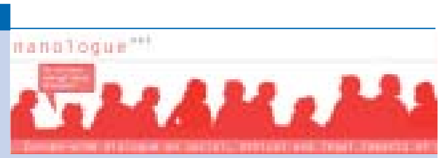
GMOS AND NANOS

Is the same contrast not found, in both debates, between the utopian promises of the advocates and the apocalyptic prophesies of the detractors? Joyce Tait, a sociologist at Edinburgh University, believes that "while it is clear that the controversy over GMOs has influenced the way nanotechnologies are perceived, the comparison does not stand up to analysis as it supposes that nanotechnologies form a coherent whole that can be judged by citizens in full knowledge of the facts". In fact, nanotechnologies cover a mixed bag of research and technological applications, some of which could be accepted and others rejected. "What is more," stresses Joyce Tait, "nanotechnologies are still in their infancy and a lot of things could change, especially as a result of initiatives for dialogue between researchers and citizens."

Let's talk nano-society

"This is the first time that scientists are turning to the media and general public to explain what they are doing at a very early stage in their research," observes Ottilia Saxl, director of the Stirling Institute of Nanotechnologies (UK). This institute plays an active role in promoting nanotechnologies – by increasing public awareness as well as supporting the sector's industrialists and academics – and was instrumental in organising the 2005 EuroNanoForum, in September 2005.

Communication with the general public is a priority of European nanotechnology policy, giving rise to diverse initiatives for dialogue between researchers and the public. There are information portals – the Nanoforum site, hosted by the aforementioned Stirling institute, for example, is a genuine showcase for European nanosciences – and travelling exhibitions offering the very best of European research in the field, such as the NanoDialogue project piloted by the Naples City of Science (IT). Exchanges between the layman and the experts are structured and organised by sociologists, for example through the Nanologue project, piloted by the Wuppertal Institut (DE), one of the aims of which is to "help researchers to understand social expectations so they can take them into account when conducting their research". One rather surprising initiative is a pack of cards, known as Democs. Developed with the aid of the New Economic Foundation in London, these offer factual information and ethical considerations and are designed to provide an entertaining way of increasing awareness.



To find out more

- www.nanodialogue.org
- www.nanologue.net
- www.neweconomics.org/gen/democs.aspx

The MIRACLE and *the infinite*

A doctor and psychoanalyst, Emilio Mordini teaches bioethics at La Sapienza University School of Medicine in Rome. Director of the Centre for Science, Society and Citizenship, he also coordinates the BIG (Bioethical Implications of Globalisation) and BITE (Biometric Identification Technology Ethics) European projects. RTD *info* talked to him about the new ethical realities and the psychological implications of the 'infinitely' small.

"Everybody agrees that there was no scientific reason for going to the Moon, but that these trips made it possible to collect some very important information. This would not have been possible if public opinion, fascinated by the mythical dimension of the project, had not accepted its phenomenal cost."

Emilio MORDINI

Above, the Moon's 'Alpine Valley', viewed by Smart-1. ©ESA

Do you believe that the current boom in nanotechnologies and future prospects raises new ethical issues?

Probably not. Nearly all the ethical issues raised by nanotechnologies – respect for human dignity and private life, social equality, limitation of military uses, alternatives to tests on animals, etc. – had already been raised by biotechnologies some 20 years ago. We just have to adapt the procedures for the evaluation of nanomedicine projects by the ethics committees, in particular by adding new competences. But that is no more than a technical adjustment. Ethical questions are rarely completely new. What is new, rather, is the conditions under which they develop and the solutions these require.

So how do you explain the concerns that are beginning be expressed?

These concerns – which are, moreover, mainly apparent in the Anglo-Saxon countries – must first be put into perspective. A recent survey commissioned by the Ecology Party in Italy, for example, showed that the vast majority of citizens were totally oblivious to nanotechnologies. Then you must look at the nature of these concerns. The most known and popularised expression of them, notably in Michael Crichton's novel *Prey*, is based on the fantasy that man-made nanoparticles could reproduce by themselves and invade the planet. For a psychoanalyst, this is a very traditional subject of myths and fairy tales: that of invisible creatures and magical objects. Again, as for ethics, there is nothing really new here. It is rather a good example of the idea that technologies can penetrate and fuel a culture.

That said, a very interesting study published by a research team from the University of North Carolina in 2004 showed that people who had read *Prey* were generally less afraid of nanotechnologies than those who had not read it. It is better to try and understand what these fears express, from the point of view of the collective imagination and unconscious, than to try and condemn their irrationality. Why are we afraid of things we cannot see or understand? No doubt for reasons linked to the history of mentalities. I find, for example, that there are great similarities between our postmodern age and the baroque age.

What kind of similarities?

In particular, the fascination, that is the mixture of attraction and repulsion, with everything to do with miracles and the infinite, including in the scientific field. In the 17th century, miracles were present everywhere in society, for both good and evil – take witchcraft, for example. As to the infinite, it was precisely at this time that people started to view it as a mathematical notion and to consider it in the context of astronomy.

Today, the infinitely small of the nanosciences has replaced the infinitely big of astronomy. As to miracles, there are the negative miracles that we have just referred to – the fear of seeing nanoparticles invade the planet, for example.

It also seems to me that our decision-makers should be ready to draw on this fascination with miracles. In the past, the portrayal of the miracle was a tried-and-tested technique of exercising power – such as the rising of King Louis XIV, resplendent every morning. The Americans used this strategy at the time of the Apollo missions. Everybody agrees that there was no scientific reason for going to the Moon, but that these trips made it possible to collect some very important information. This would not have been possible if public opinion, fascinated by the mythical dimension of the project, had not accepted its phenomenal cost.

If we really want nanotechnologies to enjoy popular support, we should not be afraid to apply this example, by appealing to the mythical fascination with the nanotechnological world. In what way? I don't know. Perhaps the image of these nanorobots, travelling through our blood vessels to repair the body from within could be compared to the symbolic dimension of the army of Lilliputians treating the body of the giant Gulliver… ■