

Great hopes for

With soaring R&D costs and a dearth of blockbuster drugs, nanotechnology could yet prove to be the saviour of the pharmaceutical industry. **Lisa Melton** finds out how

Despite revolutionary technologies in drug discovery that allow researchers to identify greater numbers of lead compounds, the biggest challenge for the pharmaceutical industry is still to deliver the right therapeutic molecule to the right spot in the human body.

Most drugs are delivered to patients with a systemic approach, that is, if you flood the body with enough active compound some of it will reach the affected organ, tissue or cell. It is an inefficient and risky strategy.

Going nano can change all that. 'Nanotechnology can turn a mediocre drug into a wonderful drug,' says Joachim Bender, ceo for NanoDel Technologies in Magdeburg, Germany. Nano structures are retained longer in blood and in tumours. They have excellent bioavailability and low toxicity. And, critically, they deliver drugs to specific areas in the body.

And there are cost savings to be had. Nano-enabled solutions could accelerate the time of bringing a new drug to market, and extend the useful life of existing drugs by allowing reformulations. In view of the numbers of drugs coming off patent, and with few new drugs in the pipeline, it is hardly surprising that the pharmaceutical community is starting to eye nano solutions with growing interest.

Nano-driven drug delivery, in particular, is likely to grow at a phenomenal pace. According to a 2005 report from an industry consulting firm, NanoMarkets, nano-enabled drug delivery systems will generate more than \$1.7bn in 2009.

Some early successes have helped raise expectations. Elan Pharma from Dublin, Ireland, is one of the first companies to nanosize drugs, and currently boasts four products on the market derived from its *NanoCrystal* technology.

NanoCrystal formulations shrink the drug's particle size, increasing the surface area, and enhancing dissociation. Paul Breen, the company's executive vice president, estimates that 40% of drug candidates fall out of the pipeline due to poor

water solubility. Elan reformulates them into particle systems to overcome this.

NanoCrystals are 1000nm in diameter, and they are produced by milling the drug molecules, which are then coated with GRAS (Generally Regarded As Safe) stabilisers to stop agglomeration. The result is an aqueous suspension of the drug that behaves like a solution and enhances oral bioavailability.

Elan's first product was Wyeth's immunosuppressant *Rapamune* (sirolimus) which received marketing approval from the US Food and Drug Administration (FDA) in 2000. *Megace* (megestrol) was approved in 2004 for patients with AIDS. The original formulation was a liquid that had to be taken with food, so thick it made patients gag. Now the reformulated compound is 16 times less viscous than the original suspension and much easier to swallow. 'We've had responses from patients saying that it's fantastic,' says Breen. 'They see a tangible benefit.'

Novavax, a Maryland-based biotechnology company, is also in the business of improving the biological performance of FDA-approved drugs and new chemical entities. Its goal is to create topical and transdermal formulations that surpass existing ones using a composite emulsion formulation of micellar nanoparticles (MNP). 'It looks like a traditional lotion or cream and is applied like one. By understanding the physicochemical properties of the formulation and matching it to the architecture of the skin we can either increase the drug's retention in the skin or maximise transdermal flux,' says Robert Lee, vice president, pharmaceutical development.

The company's first FDA-approved product, *Estrasorb*, is an MNP formulation of the female hormone oestradiol, used to treat menopausal symptoms. It was approved in 2003 and is marketed in the US by Esprit Pharma. The nano-emulsion is absorbed into the skin and gradually diffuses through the deeper layers, until it enters the bloodstream.

The particulate nature of the MNP allows Novavax scientists to tune the pharmacokinetics of the drug to extend its active life. In the case of *Estrasorb*, the pay-offs are steady plasma drug levels and a significantly increased half life of 58 hours compared to oral oestradiol, which has a half life of 17 hours.

Cancer therapy

'The Holy Grail for drug delivery is to deliver a drug exactly when and where you need it. That allows you to work at much reduced dosages, reducing toxic side effects,' says Simon Biggs, professor of particle science and engineering at the University of Leeds. Nowhere is this need more acute than in cancer therapy. The trouble with many cytotoxic drugs is that, while they wipe out dividing cancer cells, they do not spare healthy normal ones. Nanoparticle formulations can potentially overcome this quandary by providing exquisitely targeted formulations.

One such targeted cancer system has been developed by Australian company pSivida to treat advanced, inoperable liver cancer. The product is a nano-enclosed radioactive ³²P injected directly into the tumour and is currently in phase II clinical studies at Singapore General Hospital. 'The radiation only travels about 1cm in tissue, enabling localised killing of cancer cells without exposing the systemic circulation to damaging radiation,' says Mark Parry-Billings, pSivida's European director.

In brief

- Nano structures deliver drugs to specific areas of the body
- Nano-enabled drug delivery systems could generate \$1.7bn in 2009 (NanoMarkets)
- Possible application for lung treatment
- Nanoparticle drug delivery could enable insulin to be taken orally

very small things

The company's drug delivery platform, *BioSilicon*, is a biomaterial derived from elemental silicon as used in the semiconductor industry. Particles are fabricated with a 'honeycomb' matrix capable of storing an active compound in its nano-sized pockets. As the silicon dissolves, the drug is released. 'The nano-aspect is the size of the pores in that structure,' Parry-Billings points out. Adjusting the porosity of the matrix and the size of the pores alters the speed and dose at which the drug is released – ideal for controlled release systems.

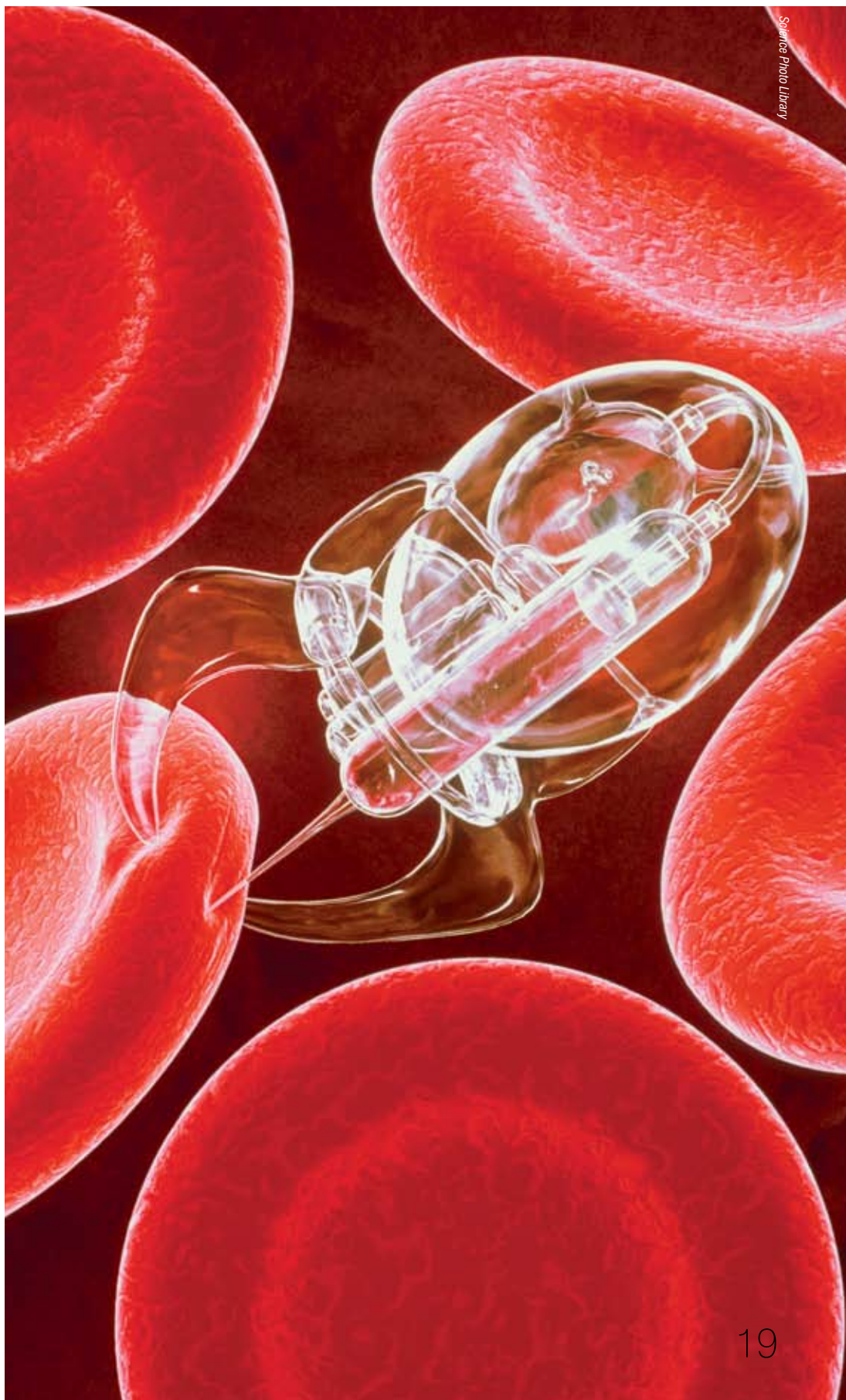
Germany's NanoDel Technologies has developed a nanoparticle formulation that shuttles cancer treatments into the central nervous system. 'University researchers discovered that nano particles could cross biological membranes, in particular the blood-brain barrier. The next step was to use them to transport drugs into the brain,' explains ceo, Joachim Bender.

Pharma researchers have always faced the daunting challenge of getting active compounds into the brain. Patients with glioblastomas, an aggressive form of brain tumour, for instance, normally die within 12 months of diagnosis because chemotherapeutic compounds like doxorubicin fail to reach the tumour.

The system developed by NanoDel consists of the active drug adsorbed onto polybutylcyanoacrylate nanoparticles and the resulting complex is coated with a surfactant. The particles are injected into the blood circulation and taken up through endocytosis by the brain's capillary system. Once in the brain, the polymers are degraded by hydrolases and the particles deliver their cargo. The breakdown products are water soluble and excreted with urine.

Following successful preclinical studies, the company expects to start clinical trials in 2008, though NanoDel has no plans to market these nano-polymers directly. Instead, it will co-operate with partners from the biotech and pharmaceutical industry through licensing agreements.

Another company striving to develop targeted oncology drugs is NanoMed Pharmaceuticals, from Kalamazoo, Michigan. 'We set out to develop a drug



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delivery technology that would be fast, flexible and cost efficient,' says company co-founder, president and ceo Stephen Benoit. 'Our *Nanotemplate Engineering* platform literally takes a few minutes to make solid nanoparticles smaller than 100nm in size, and it involves mixing all the ingredients in a single vessel,' Benoit explains.

NanoMed's formulation entraps various active ingredients in nano-sized spheres which can be targeted to specific tissues, cells and tumours. 'The key is selecting the appropriate lipids and surfactants which, when heated to form a microemulsion, can then be cooled directly to form nanoparticles,' Benoit divulges.

Tweaking the formulation enables NanoMed scientists to improve the uptake in target cells. 'We can attach specific ligands that will be attractive to a particular type of tumour,' says Benoit. But what gives NanoMed technology the edge over other nano-formulations is the ability to overcome multidrug resistance, by avoiding the efflux mechanisms that try to keep the drug out of the tumour.

The company's lead product is a drug to treat acute myelogenous leukaemia. Many leukaemia patients are elderly, and so more resistant to chemotherapy, so the outcome is often poor. An efficacious, relatively non-toxic approach could change treatment prospects dramatically. Although the drug is currently in pre-clinical development, NanoMed plans to begin safety and efficacy tests in leukaemia patients in early 2008.

Patient acceptance of nano-medicine is soaring. In fact, the high US demand for *Abraxane*, a nanoparticulate formulation of the widely-used breast cancer drug taxol, has erupted in controversy. The new cancer treatment, *Abraxane*, developed and marketed by a California-based company, Abraxis BioScience, received FDA-approval in 2005 for use in patients with metastatic breast cancer. But \$4200/dose for *Abraxane* when Taxol's generic form, paclitaxel, sells for just \$150, is a hefty price tag.

The company defends the jump in price because *Abraxane* causes fewer allergic reactions in patients than the older medication. The old version must be mixed with toxic solvents limiting the amount patients can receive. *Abraxane's* nano-sized protein albumin particles deliver the therapeutic cargo straight into the vascularised tumours, boosting the amount of drug available to combat cancer cells by 50%.

No needles

When it comes to vaccines, nanoparticles may prove to be the ideal adjuvant. Most vaccines need an adjuvant to trigger an immune response. In the US, the only adjuvants approved by the FDA are aluminium salts which produce irritation and inflammation around the injection site. Biosante, from Georgia and Pennsylvania, US, is developing calcium phosphate nanoparticulate technology as an adjuvant for use in human vaccines. According to Tulin Murcol, Biosante's director of drug and vaccine delivery, the company's nanoparticles, when combined



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with most vaccine agents, boost the immune response 50 to 100-fold. Using them as vaccine adjuvants would allow low dosages, and improve safety.

The company has already tested the nanoparticles in healthy individuals in phase I trials, using both injectable and needle-free routes. Not only is calcium phosphate a natural component of the body, and thus biodegradable, but there is an added advantage. 'The calcium phosphate particles, as opposed to alum, can be lyophilised or spray-dried into powders,' says Morcol.

Chinese scientists have this year reported results from nanoparticle drug delivery system which would allow insulin to be taken orally. Hsing-Wen Sung and colleagues at the National Tsing Hua University devised a way to load insulin onto nanospheres made of chitosan, a natural carbohydrate polymer obtained from shrimp shells. When given to diabetic laboratory rats, the insulin-loaded nanoparticles reduced blood sugar levels in the animals. The researchers believe that these non-toxic nano-sized particles are protecting insulin from destruction in the stomach.

Nano-sized carriers could become all the rage as drug delivery systems for the lungs. The advantages over conventional inhalation systems are manifold: biodegradable nano-size carriers can be formulated to target specific areas of the lung, and may not be cleared or inactivated as quickly as conventional medi-

cines. What's more, these nanomedicines could be designed to deliver their drug cargo over a controlled period, reducing the frequency with which patients have to inhale their medicine, says Lea Ann Dailey, a pulmonary drug delivery researcher at King's College, London.

Dailey became concerned at reports from environmental toxicologists describing the inflammatory effects of airborne ultrafine polystyrene particles which showed that the large surface area of tiny particles alone triggers lung inflammation. If so, using nano-carriers for lung delivery would have no future. But it was also possible that the non-biodegradable nature of these environmental polymers was causing the damage.

Dailey found that biodegradable particles of the same size and surface area as non-biodegradable ones did not summon an inflammatory response. These are preliminary studies, Dailey warns, and it is premature to reach a verdict over long term safety without intensive toxicological studies.

While uncertainty over the environmental health and safety of nanotechnology prevails, it is worth remembering that what we call 'nanotechnology' has been around for a long time. From car catalysts to detergent, humans have been exposed to nano-scale materials for decades: they just did not call them 'nano'.

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