HIV genes. The use of protease inhibitors, together with nucleoside analogues, is relatively successful at reducing the viral load to undetectable levels, but HIV exhibits a high level of antigenic variation leading to the increased generation of drug-resistant strains. In fact, ~25% of the 3000 new cases of HIV diagnosed in the UK each year are infected by drug-resistant strains. A potential anti-HIV drug based on the inhibition of Tsg101 and other targets is, therefore, particularly attractive, as Myriad's president Adrian Hobden points out. 'The search for drugs to block cellular proteins that are taken over by the virus has one potential major advantage; the target here is a host protein, not a viral protein, so we hope that the virus will not find a way to get around it quite so easily,' he predicts.

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Holey chips for drug delivery

Sharon Kingman, Freelance writer

Small pellets of porous silicon have been developed that could make targeted drug delivery and diagnosis a much simpler process. Implanted under the skin, these pellets could monitor blood levels of an administered drug, release new doses when necessary and then completely dissolve once empty.

pSiMedica (Malvern, UK) was set up as a joint venture in August 2000 by the UK's Defence Evaluation & Research Agency (DERA; Malvern, UK) and Sumich Group (Perth, Australia) and has already patented a form of porous silicon (BioSilicon™), which is both biodegradable and biocompatible. The company hopes this invention could help to solve many of the existing problems with drug delivery: these include noncompliance, painful injections and adverse effects resulting from the systemic bioavailability of the drug.

Leigh Canham, Chief Scientific Officer of pSiMedica, said: 'We are optimistic that this type of porous silicon gives us a material platform that is very flexible. We can tune the rates at which it degrades by altering its microstructure and varying pore size and pore density. The pore size distribution and the porosity that you achieve can be varied by changing anodization parameters like silicon resistivity, electrolyte composition and current density.' He emphasized that, unlike biodegradable polymers, the chemistry of porous silicon does not have to be altered to achieve different rates of degradation – a distinct advantage when it comes to applying for regulatory approval.

Porous silicon

Silicon is, of course, the raw material for the silicon chip and semiconductors. It can be produced to a high level of purity and is relatively cheap: even a highly pure form of silicon (99.99%) costs less than US$30 per kilogram. Canham began studying silicon while working at DERA, where he was involved in a project to develop a silicon laser.

However, after extensive reading around the subject, Canham noted some similarities between porous silicon and bioactive ceramics, which were being investigated for orthopaedic applications. This led him to investigate whether silicon could be biocompatible. To his surprise, *in vitro* tests showed that thin layers of highly porous silicon could completely dissolve away in simulated body fluids[1]. Subsequently, a six-month study using guinea pigs showed that solid silicon implants could persist in the body without rejection, whereas implants of porous silicon continuously decreased in weight over the study period[2] (Fig. 1). Canham, together with collaborators at St Thomas's Hospital (London, UK), have shown that porous silicon will break down in the body into the harmless compound silicic acid, which is present in many foods and drinks (Canham *et al.*; unpublished data).

Drug delivery

Silicon can be made porous by either electrochemical or chemical etching[3] and these techniques can be used for both silicon wafers and silicon powders. However, Canham pointed out that 'For many drug delivery applications, you do not necessarily want chips or segments or wafers – you want microparticles or nanoparticles. You can either start with a silicon film, porosify it and process it into a powder, or you can begin with silicon powder of the required size and shape and porosify that. We are investigating both options.' Powdered porosified silicon could, he said, be incorporated into ordinary capsules for oral delivery, into patches for transdermal drug delivery or into microparticles covered with the appropriate antibodies that could be injected into the bloodstream, for example, to lodge in tumours.

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pSiMedica is currently considering delivering cytotoxic and anti-inflammatory agents in BioSilicon. Canham said: 'We are addressing issues common to any new drug delivery system. Can we put enough drug within porous silicon, which has very small pores? Once it is in the body, can we release the drug in a controlled and sustained manner? What is its shelf life? Most importantly, we have to get the kinetics right for the application concerned. We have started looking at these issues but there is still an enormous amount of work to do.'

Diagnostic tool

Porous silicon also has significant potential in a range of therapeutic areas, including diagnostics[4]. While studying silicon at DERA, Canham noticed that highly porous silicon would luminesce. Therefore, Canham and his collaborators have been developing biodegradable mirrors with both diagnostic and therapeutic applications[5]. Such mirrors could be implanted under the skin to monitor the recurrence of cancer, for example. Canham said: 'You load the mirror with appropriate antibodies and, if antigens from cancer cells bind to them, this will change the reflectivity of the mirror, which can be optically monitored.'

Optical monitoring of drug delivery could follow, he said. 'If the mirror was loaded with the drug, you could optically interrogate it at intervals to see how fast it was dissolving *in vivo*. Its reflectivity spectrum would tell you exactly how many layers of the mirror were left.'

Ijeoma Uchegbu, Senior Lecturer in Drug Delivery at the University of Strathclyde (Glasgow, UK) commented that the idea of a responsive unit that combined both diagnostic and therapeutic capabilities was very interesting. However, she suggested that, 'The reaction of the regulatory authorities to 'biodegradable silicon' may, however, prevent a speedy application of this technology.'

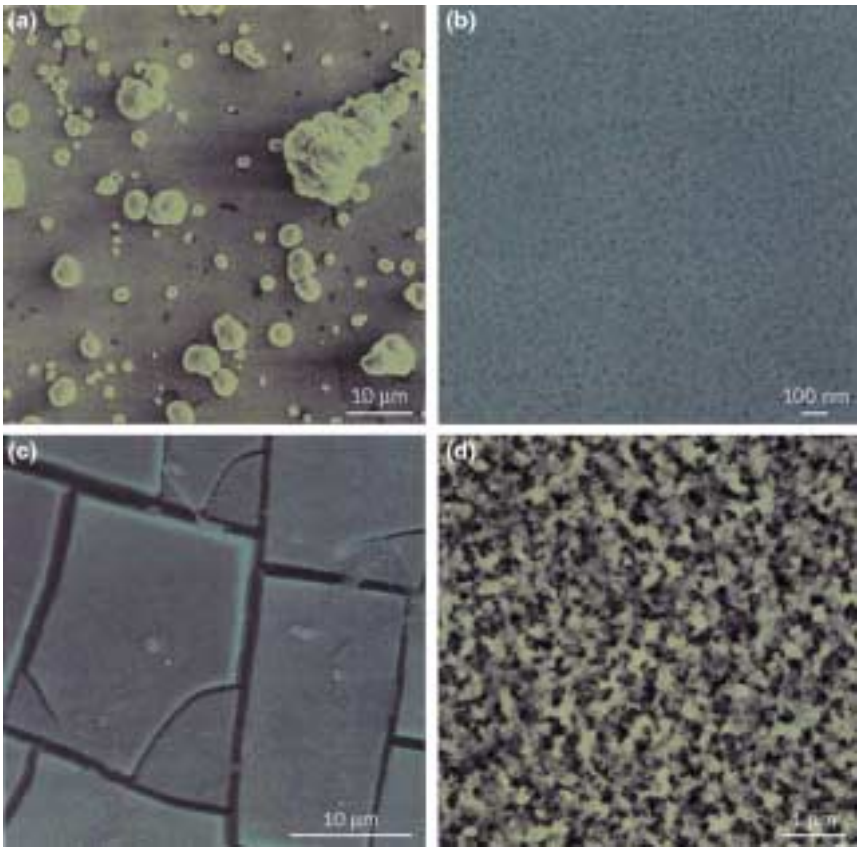

Figure 1. These scanning electron microscopy images show how the surface of porous silicon interacts with various body fluids. In each case, the silicon was incubated at a temperature of 37°C. **(a)** After two weeks in human plasma the surface has started to become covered by the inorganic phase of bone. **(b)** After 67 h in gastric fluid, the existence of individual pores is evident, although the level of corrosion is minimal. **(c)** After six hours in intestinal fluid, corrosion has resulted in cracks appearing after removal. **(d)** After two weeks, in cerebral spinal fluids there is evidence of corrosion. Because corrosion takes place in each fluid – apart from gastric juices – porous silicon can be said to be a genuine biodegradable material. Figure kindly provided by Leigh Canham (pSiMedica, Malvern, UK).

Canham, however, remains optimistic that it could be possible to begin clinical trials for applications involving delivery of cytotoxic drugs for cancer therapy by 2003.

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