SILICON TECHNOLOGY AND PHARMACEUTICS

– *an impending marriage in the nanoworld*

The recent discovery that, following nanostructuring, silicon can be rendered biocompatible and biodegradable has far reaching and profound long-term implications for the pharmaceutical industry and, indeed, medicine as a whole.

by Professor Leigh T. Canham, Dr Roghieh S. Saffie, Stephen E. Connor and Dr Roger Aston

Nanostructure science and technology is the design, fabrication, understanding and use of materials at length scales between 1 and 100 nanometres. It has the potential to extend both the way in which materials and products are created, but also the functionality of those materials. Analysts believe that there are only a few areas of nanotechnology that will mature to the market over the next 2-3 years. Despite this, there are good grounds to predict that the technology will have significant, if not profound, effects on how we might administer our drugs of the future as well as the manner in which we treat tissues in surgery, orthopaedics, and tissue engineering. Current R&D on nanoscale science and technology is also expected by most scientists working in the field to eventually have major effects on many other technologies outside pharmaceuticals.

Molecular nanotechnology has been described as the process of positioning atoms or molecules to produce nano-devices with some level of molecular/atomic precision. The application of this process to medicine, or nanomedicine, is being explored with a variety of materials including polymers, ceramics, metals and now semiconductors. The aim here is to provide a cell or tissue interface that confers a level of bioactivity or functionality not achievable in the absence of the imparted nanostructuring. The recent discovery that the principal semiconductor, silicon, can be rendered biocompatible and equally importantly, biodegradable, following nanostructuring opens up interesting opportunities. This impending marriage between the electronics and pharmaceutical sectors has far reaching implications because of the vast applicability that silicon-based electronics has found in our everyday lives[1].

We would like to draw some links here with how semiconductor technology has and will continue to evolve into the nanoscale. One might then also speculate as to how the 'silicon roadmap' will have significant effect on the pharmaceutical one, and over what timescales. Prior to doing so, we would like to highlight some of the drivers that are leading medicine into the Nanoworld more generally (**Table 1**).

Table 1
Drivers of nanotechnology in medicine

Tissue Engineering	Artificial nanoscale building blocks may one day be employed to repair tissues such as cartilage, bone and skin
Drug Delivery	Nanostructures may be used to deliver drugs where they are required avoiding harmful side effects
Diagnostics	Nanotags or labels may make diagnostics quicker and more specific
Drug Screening	Nanotechnology may find use in research systems to accelerate screening and detection

Using nanotechnology

It's a matter of scale

When we consider the architecture of the biological building block, the cell, it is clear that life runs on massively parallel events at the micro, nano and molecular scales (**Figure 1**). The results of these

processes, of course, manifest at the macroscale through the structure and function of organs and finally the body itself. Nanostructured materials provide a 'link' between the macro and the nano in a manner not previously achievable. That is, a device can be engineered at the macroscale (eg replacement hip or other tissue or organ), while through nanostructuring such a device can also offer a scaffold or template for a variety of biological structures and/or functions at the molecular or cellular level. Thus, the key attributes sought in a material are the ability to impart nanoscale 'order' and nanoscale 'control', a process that has also been described as programmable positional control. Both flexibility in the order and control of nanoscale manufacturing are important in providing a versatile template for the building of biological structures to support the 'drivers' in medicine listed in **Table 1**.

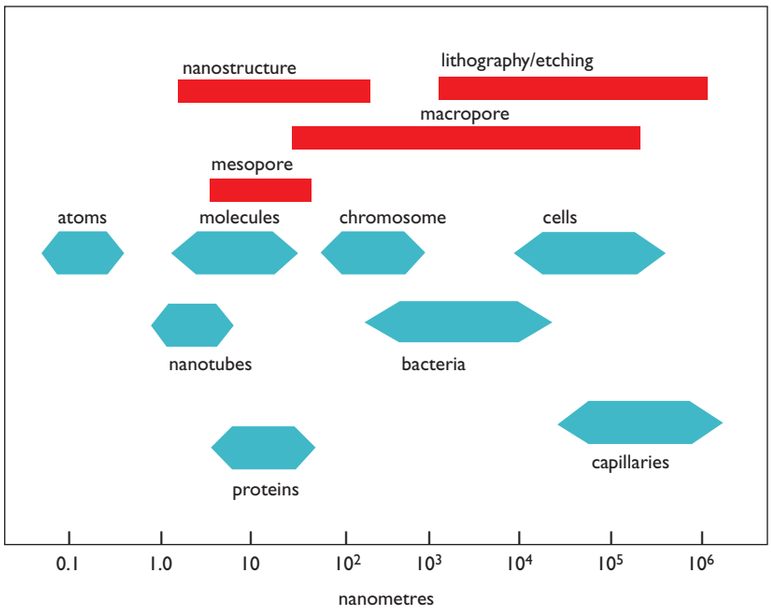


Figure 1
Dimentionality in the biological world

Nanostructuring techniques: bottom up or top down?

Bulk nanostructured materials are defined as solids with nanoscale or partly nanoscale structuring within. Why nanostructure materials? There are now two fundamental driving forces here; enhanced performance or radically novel performance. Examples of the former are the improved hardness, strength or toughness of ultrafine grained metallic materials. An example of the latter which we discuss in the 'Using silicon nanotechnology' section is the nanostructuring of silicon which brings novel optoelectronic and biochemical activity.

There are two approaches to realising a nanostructure. One is the self-assembly of molecules (the 'bottom-up approach') that is popular with biologists and chemists. This is the basis of most gas phase 'cluster science' and 'nanocrystal' synthesis via chemical routes. The other is the breaking up of a bulk structure into nanosize units (the 'top-down approach') that is popular with solid state physicists and engineers. Here techniques such as mechanical milling, chemical etching, lithographic patterning and micromachining are utilised, often in combination. Nanophase Technologies Inc has scaled up a physical vapour process to generate nanoparticles at the ton rather than gram level creating the capability to service global markets for devices.

Tissue engineering

One of the principal areas where nanostructuring is making significant impact, as witnessed by the number of companies presently applying nanostructuring techniques, is in tissue and organ engineering. The demand in this area of course, comes from the population itself: the numbers of individuals waiting for suitable organs for transplant continues to rise with more than 75,000 people presently on waiting lists in the US alone. Bio-artificial devices provide an avenue to address these current shortages.

Perhaps the greatest the challenge for the tissue-organ engineer is the creation of a suitable blood supply to provide vital nutrients, oxygen and metabolic exchange. To meet this challenge scientists have attempted to grow cells on biodegradable scaffolds incorporating angiogenic factors for blood vessel growth. In other studies, a blueprint of the desired vasculature is engineered *in vitro* through microfabrication of a biodegradable scaffold. By adopting lithographic techniques and micromachining, three-dimensional scaffolds are produced to act as templates for cellular-seeding. Application of endothelial cells to such scaffolds has produced microfluidic channels as small as 15 microns in diameter with the walls coated in endothelial cells. Cells have been shown to react to topography on the nanoscale as well as microscale. These reactions can be exploited in directing cell behaviour via, for example, patterned adhesion or activation of cell movement. If the topography is made in a biodegradable surface, it could be tuned to disappear once the desired cellular response has been initiated.

Drug action

Nanotechnology should provide even further insight by probing drug-induced changes within the cell itself. We are now able to view the chemical processes and microscopic structures of living biological cells at unprecedented resolution. The atomic force microscope can locate and measure the extremely small forces that accompany the receptor-ligand binding event on a cell's surface membrane. Our microelectrodes can detect the exchange of ions between the cytoplasm and the extracellular matrix[2]. Confocal optical microscopes, when teamed up with fluorescent probes can track chemical processes throughout the cell. This nano-instrument toolbox has the potential to improve our understanding of drug metabolism and effects, beyond the cellular level to that of individual organelles.

Drug design

Many of the molecular events in a cell take place within the confines of structures such as membranes, organelles or multi-molecular complexes. The production of a variety of nanoscale surfaces may one day provide a suitable 'test-tube' to mimic and monitor molecular events occurring at surfaces of membranes or other organelle structures. A good example of computational research at the nanoscale is that of 'minimal vaccine' design. Here, companies such as Pharmacia Corp are modelling the fate of fragments of proteins associated with tumour cells. Once taken up by cells and digested, a fraction of the resulting short fragments, (epitopes) become attached to MHC complexes and exported to the outer cell membrane. The immune system is then triggered to attack the invading tumour cell with lymphocytes. This induced biological response forms the basis of one area of protein-based cancer therapy; that of polyepitope vaccine design. Desired sequences must be not only biologically active but also amenable to large-scale production, storage and delivery.

Drug delivery

For much of the industry's existence, pharmaceuticals have primarily consisted of simple, fast-acting chemicals that are dispensed orally (as solid pills or liquids) or as injectables. During the past three decades, however, formulations that control the rate and period of drug delivery and target specific areas of the body for treatment have become increasingly common and yet complex. The existence of more than 200 specialist drug delivery companies bears witness to this. The development of a new drug involves more than the synthesis of a substance that has a particular effect on the body. The developer must also consider how to transport the drug to the appropriate part of the body and, once there, make it biologically available for use. This is not a trivial issue; in some cases, realising the appropriate system can be as difficult as developing the drug itself. For example, many drugs' potencies and therapeutic effects are limited or otherwise reduced because of partial degradation that occurs before they reach a desired target in the body. Indeed, many drugs can be delivered by several routes each with their own advantages and disadvantages.

In an ideal drug delivery system, the drug profile in the desired tissue will be maintained at optimum therapeutic concentrations with minimum fluctuation, predictable and reproducible release rates for extended durations. Currently several approaches are being pursued for improved delivery of therapeutic products.

Table 2
Carrier systems for drug delivery

STRUCTURE	SIZE	CHARACTERISTICS
Nanocapsules	(50-200nm)	Drug core surrounded by a layer acting as a temporary barrier to drug dissolution or diffusion
Nanoparticles	(25-200nm)	Continuous matrices containing dispersed or dissolved drug
Vesicles	(25-3000nm)	Single or multi lamellar bilayer spheres containing the drug in their lipid or aqueous regions
Low density lipoproteins	(20-25nm)	Drug is adsorbed on to the protein head groups, solubilised in the lipid core or attached to the surface
Nanoemulsions	(20-50nm)	Drug in either or both oil and aqueous phases

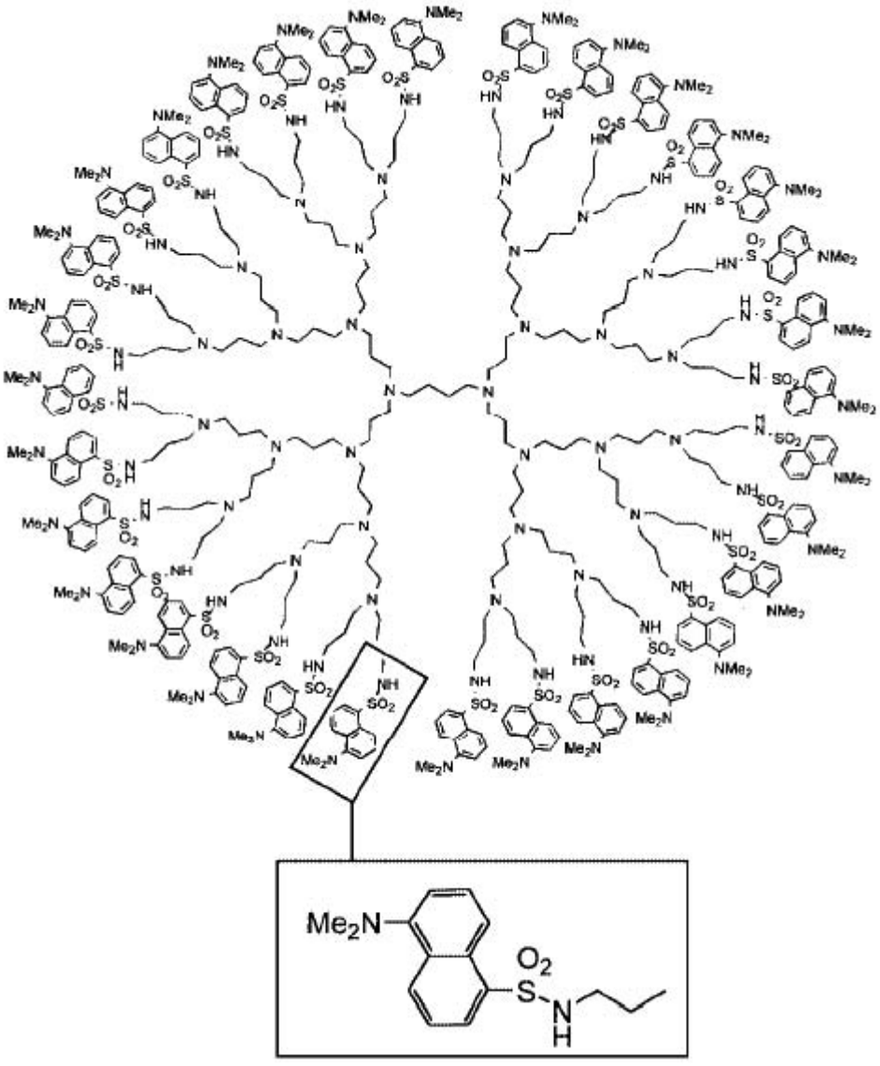


Figure 2

Most controlled drug delivery systems under development today operate at the microscale. However there is a growing realisation that nanostructuring of drugs and nanoparticle carrier systems have a lot to offer. Firstly, a range of drugs can have their solubility greatly raised by converting microparticles to nanoparticles. In many such instances, poor water solubility correlates with poor dissolution rate, and decreasing particles size increases the surface area, which leads to an increase in dissolution rate. Secondly, biodegradable carriers in nanoparticle form in principle offer systemic distribution and targeting since their size and surface chemistry can be tuned to avoid the reticulo-endothelial system which scavenges foreign particles.

Conventional approaches to nanoparticulate carriers, including polymeric nanoparticles and liposomes (**Table 2**), do however have the following limitations:

- Relatively high costs of production.
- Physical processing that can be harmful to the drug.
- Low drug encapsulation efficiency.
- Use of toxic solvents/reagents.
- Limited ability to realise sub 80nm particle formulations.

The pharmaceutical giant Merck, for example, is assessing the unique issues involved in incorporating nanosized particles in dosage forms. Such forms offer higher solubility, better dose uniformity, enhanced bioavailability and when taken orally, fewer food effects. Indeed several

companies are active in this field and are exploring different technologies to reduce particle size in the nanoscale. Examples include the use of supercritical fluids, grinding techniques and high pressure homogenisation[3].

One well-developed bottom-up approach is that of creating dendritic polymers or 'dendrimers'. These polymers are synthesised as monodisperse rod-shaped or spherical structures ranging from 1 to 20nm diameter (**Figure 2**). Molecular weight and the number of terminal groups increase exponentially as the number of layers of the polymer. Dendritic macromolecules are available commercially in kilogram quantities and produced under GMP. Dendrimers have had drugs encapsulated within their core and had their outer shell conjugated with antibodies, chromophores and other photosensitisers that facilitate targeting, tracking and remote activation respectively. Dendritech Inc is an example of a company developing such nanomolecules for pharmaceutical use.

Targesome Inc is developing nanoparticles constructed with bipolar lipid subunits containing a polymerisable functional group. Exposure to UV light generates spheres whose surfaces can have specific targeting agents such as monoclonal antibodies attached. The company's drug delivery devices are being developed for cancer applications through a collaboration with Merck whereby targesome particles are formulated with anti-angiogenisis factors from Merck. Such targeted nanoparticles are expected to have improved toxicity to tumours through the multivalent nature of their surface.

Silicon – bridging gaps in the medical nanoworld

Since the invention of the integrated circuit in 1959, the complexity and thereby operating speed of silicon 'chips' has seen outstanding improvement at a rate governed by 'Moore's Law'. This refers to an early predictive statement that industry investment into further and further miniaturisation would allow us to roughly double the number of transistors per unit area on a chip every year[4]. Increasing the packing density of the basic building blocks of a circuit can only be achieved by higher and higher resolution patterning ('lithography') that determines the minimum feature size. As a result, leading edge companies now manufacture silicon devices with feature sizes below 180nm and Moore's law looks set to hold for one more decade before basic physical limits preclude further miniaturisation. The Semiconductor Industry Association (SIA) regularly publishes a roadmap that outlines the advances in technology required to continue its historical rate of productivity improvement of 25-30% per annum. By 2014 we will be at the physical limit of the CMOS (Complementary Metal Oxide Semiconductor) transistor with a gate length of 20nm and an oxide barrier of 0.5nm, about two atoms thick. We already know how to pattern silicon at the 100nm level by extensions of optical lithography. One of the many technical challenges is to print 10nm features in a cost-effective, high throughput manner. Hewlett-Packard, IBM and Intel for example, are nevertheless already committed to nanoscale silicon processing. This Summer Intel researchers announced its first 20nm transistor, targeting a microprocessor that will contain a billion such devices and run at speeds of 20 gigahertz. What this demonstrates is that the mainstream electronics industry is marching steadily into the nanoworld: microelectronics is already on the verge of becoming nanoelectronics.

It is not surprising that silicon is now making a major debut in the therapeutics sector – of course, silicon has been doing this indirectly for many years through the numerous electronic products and devices that are used every day in hospitals (eg pacemakers, anti-arrhythmia devices, table top drug infusion devices, etc). However, it is the coupling of the electronic properties of silicon with the ability to miniaturise that is now paving the way to a new era in 'implantable' medical products. In addition to the 'smart' properties of the element that permit the fabrication of devices based on the microchip, silicon-based MEMS offer the potential for small devices with minimal power consumption, high reliability and a potential level of regulation that leaves many current drug delivery technologies standing still. Up until now, the major drawback of

Table 3
Silicon – properties and scope

PROPERTY	POTENTIAL SCOPE
Semiconductivity	Microelectronics and oscillator-based timing accuracy
Crystal stability	Thermally and mechanically robust structures
Micromachinability	Microsensors and microactuators
Purity	Electronics-grade silicon has a purity that would be the envy of most pharmaceuticals (99.99999%)
Luminescence	Visibly fluorescent particles through nanostructuring
Light absorption	Photodiodes for the visible/near infrared
Light reflectivity	Mirrors via nanostructured multilayers
Biocompatibility	A relatively bioinert material for tissue interfacing
Biodegradability	Nanostructured silicon will degrade without apparent toxicity *in vivo*

silicon has been that it has never been considered a 'bio-friendly' material. Recent research suggests that silicon is not only bio-friendly but also potentially lends itself to an array of applications based on the novel properties following nanostructuring; these include, drug delivery, tissue engineering and diagnostic functions in the body (Physics World, New Scientist). The key properties of silicon that are now coming together to provide a tantalising array of possibilities are summarised in **Table 3**.

Using silicon nanotechnology: the pSiMedica approach

Over the last decade there has been increasing interest in rendering the semiconductor highly porous by electrochemical etching techniques[5]. Using hydrofluoric acid-based solutions, nanometre-size pores with exceptionally high aspect ratios can be generated in silicon wafers, 'chips' or particles, and with a high degree of control (**Figure 3**). The resultant material is still pure silicon, but it behaves very differently to non-porous 'bulk' silicon; one important example being that it becomes strongly fluorescent in the visible. In fact it is this light-emitting property that has attracted the attention of most physicists and semiconductor engineers to date.

The first investigations on how nanostructured silicon might behave within biological environments were carried out in Malvern, UK in 1995. It was during such studies that we made the striking observation that thin layers of highly porous silicon or polycrystalline silicon of nanometre size grains could actually dissolve completely away in simulated human plasma. In other words, nanostructured silicon was shown to be biodegradable *in-vitro*[5]. The behaviour of porous silicon in other simulated body environments has now also been assessed, as well as its biodegradability tested *in vivo*, in the subcutaneous site. The latter six-month study has demonstrated for the first time that the dominant semiconductor can be simultaneously biocompatible and biodegradable.

How might biodegradable silicon be used in pharmacy and what are its perceived merits over existing pharmaceutical materials? We will address such questions by sketching out our current R&D pSi pharmacy roadmap over the coming years:

Step 1: Microengineered control & versatility

Initially we plan to utilise the combined micromachinability and biodegradability of silicon to realise a range of BioSilicon formulations that offer highly controlled kinetics of drug release, each tailored for a different mode of administration. Control over porosity on the nanoscale is combined with control over particle size and shape. Biodegradable ceramics and polymers are not as suited to the precise photolithographic patterning of the semiconductor industry as silicon, for which such processing has been optimised in the first place. A micromachined porous tablet could contain a multitude of reservoirs within, for example, as shown in **Figure 4a**, to deliver a cocktail of drugs in a predetermined sequence. Simple electronic control could be overlaid as demonstrated in **Figure 4b**.

Step 2: Biochemical targeting & electrical control

The first phase of BioSilicon formulations above offer high precision over drug release kinetics but not the targeting nor the *in situ* versatility that biochemical modifications and electrical control offer respectively. Porous silicon has been shown to be amenable to derivitisation, replacing the unstable silicon hydride bonds by Si-C bonding with a broad range of functional group attachments[6]. This means that drugs can be covalently attached to the Si skeleton of a microparticle or nanoparticle via an enzyme-sensitive bond for example. It also means that linked antibodies on the porous particle exterior could act as targeting agents in a similar manner to Targesome particles.

Porosified Silicon (90%)

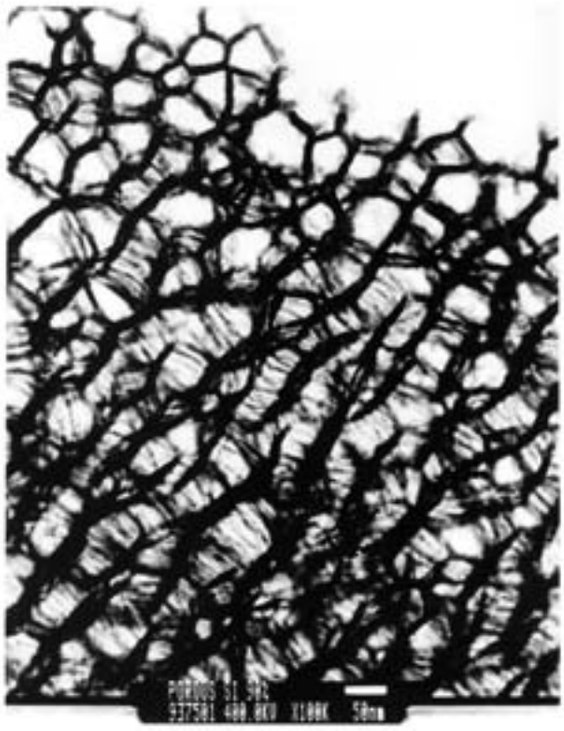


Figure 3
Cross section of 90% porous silicon. Drink coaster size of 90% porous Silicon has the same surface area as a soccer field

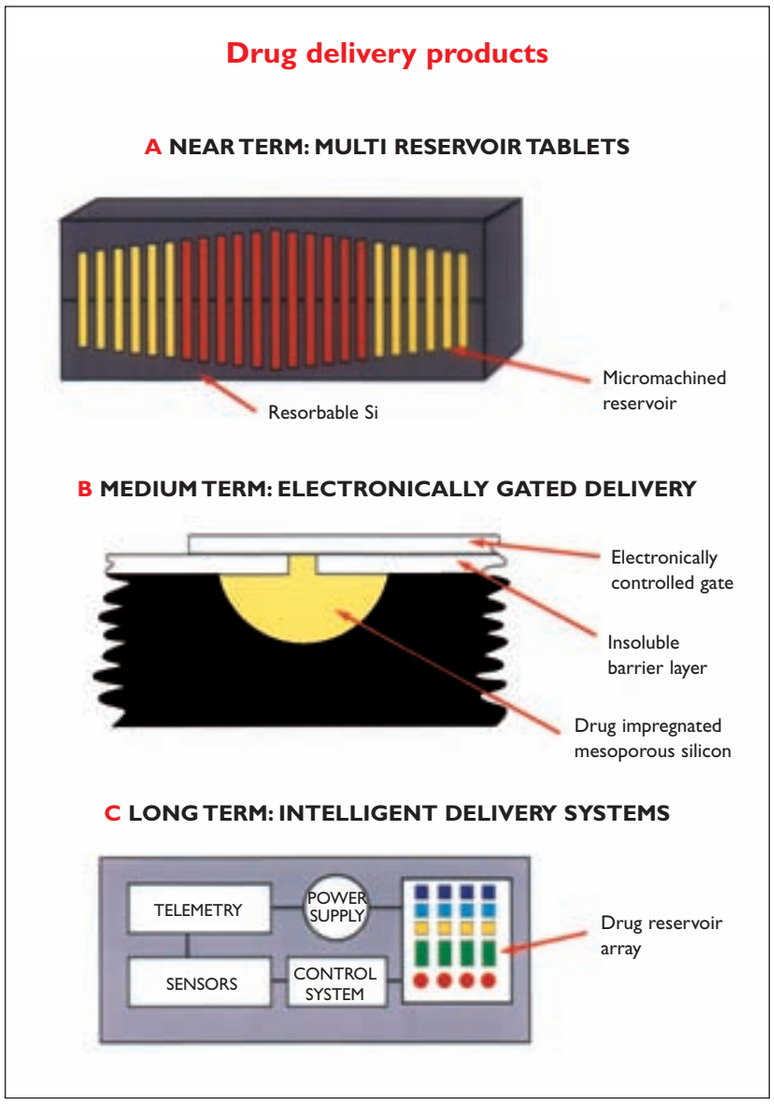


Figure 4 The SynchroMed system from Medtronic Inc provides a good example of the capabilities of implantable microelectronics in drug delivery[7]. More than 30,000 such pump-based units have been implanted since FDA clearance in 1988; the predominant users being cancer patients with intractable pain. An implanted pump has a much lower probability of inducing infection than one that is worn with a transcutaneous link, and with an in-dwelling catheter delivers the drug to where it is most needed. Microelectronic control over the pump provides programmable and versatile dosing regimes that can be tailored by the physician to match an individual's needs. The Medtronic system is a hybrid one that hermetically seals the pump and electronics within a titanium package.

Step 3: Closed physiological loops

Imagine a pacemaker that realises you are going to get breathless; a hip implant that informs you it is becoming infected or starting to loosen, a stent in which a blockage is developing. The former products are already being developed by the addition of sensors such as accelerometers to the therapeutic device; their circuitry analyses *in vivo* data and automatically raises the level of pacing to that needed for running up the stairs.

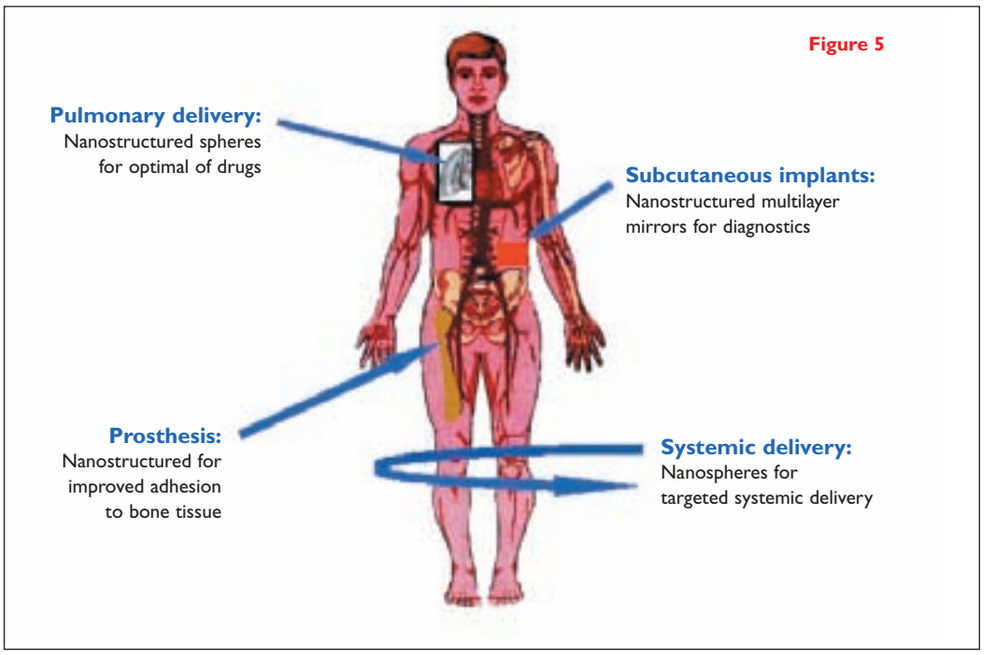
The dream of 'closed loop' drug delivery systems (**Figure 4c**) that automatically release drugs only when needed are still years away but remain very attractive. The major problem has been the *in vivo* sensor part of the system[8]. A fully integrated silicon system is still the most attractive and power supplies, pumps, filters, capillaries with decision-making circuitry have all been miniaturised on-chip to varying degrees. Such systems would, like the organs of our body, have biofeedback control mechanisms.

Nevertheless, for artificial organ development and monitoring, silicon technology is quite unique here in potential. A summary of the potential applications of nanostructured silicon in man is shown in **Figure 5**.

Conclusion

The silicon integrated circuits in our PCs are soon going to qualify as nanostructures and the ability of engineers to sculpt this material at the nanoscale as well as the microscale will have profound long term implications for medicine. If one must implant a prosthesis in the human body, it should be as small and as smart as possible. The staged application of microtools of the semiconductor industry – lithographic control, micromachining, electronic regulation, sensor-based feedback, when combined with a biodegradable platform via nanostructuring, have a lot to offer the pharmaceutical industry. In chronological terms, we expect the short-term applications of nanostructured silicon in drug delivery and tissue engineering to precede the longer-term introduction of the truly 'smart' implantable device. DDW

Professor Leigh Canham *has spent the last 14 years conducting research on differing aspects of silicon semiconductor technology. He was trained in the Department of Physics and Astronomy at University College London (BSc, 1979) and the Department of Physics Kings College London (PhD 1983). He joined the Electronics Sector of DERA in 1986 and became a DERA fellow in 1999. He has made two seminal discoveries in his career to date;*



that silicon can emit light efficiently in 1990; and that silicon can be rendered biocompatible in 1995. His 100+ publications on nanostructured silicon are the most highly cited worldwide on this topic. He holds more than 15 international patents relating to porous Si and has co-chaired more than eight international conferences and given more than 70 invited talks. In March 1999 he was awarded an honorary professorship by the University of Birmingham. Within the last four years he has given more than 10 invited talks and seminars on the medical applications of Si technology and was recently elected to the editorial board of a new international journal Biomedical Microdevices.

***Dr Roghieh Saffie** graduated with a First Class Degree in Pharmaceutical Sciences and obtained a PhD in drug delivery from the London School of Pharmacy in 1998. She subsequently joined Dompe SpA, Italy where she was rapidly promoted to head of their new facility for drug delivery research. Roghieh worked also at Moorfields Eye Hospital in various departments including Production lab, QC and dispensary for several years. Roghieh joined pSiMedica Ltd as Head of Formulation in September 2001.*

***Stephen Connor** is an experienced manager with extensive knowledge of the pharmaceutical and biological industries, including biomaterial R&D for both early and late phase clinical trials. He has wide practical experience of contract product development and production throughout Europe and the USA, as well as both large and start-up company environments. After graduating in microbiology, Steven worked at the Withington Hospital, Manchester from 1978-1985. He then held increasingly senior positions in Cambridge at Murex Medical Research Ltd, Quantum Biosystems Ltd, Cantab Pharmaceuticals Research Ltd, Chiroscience R&D Ltd, and most recently, Imutran Ltd – a Novartis Pharma company. Stephen joined pSiMedica Ltd, as Chief Operating Officer in November 2001.*

***Dr Roger Aston** has spent the past 20 years in various aspects of the pharmaceutical and biotechnology industries. He received his BSc (Hons) and PhD degrees at the University of Manchester (1975-1981) after which he spent four years at the Wellcome Foundation (Beckenham, Kent) and two years at Coopers Animal Health (a joint venture between ICI and Wellcome). He joined Peptech Limited in Australia (1987) where he became Head of the Group's Research and Development activities. In 1991 he returned to the UK and founded Biokine Technology Limited. In 1995 he was invited back to become CEO of the Peptech Group of companies. During this period, Roger Aston was also CEO of Cambridge Antibody Technology. In 1999 he joined Cambridge Drug Discovery Limited as its Chairman. He is currently CEO of pSiMedica Ltd.*

References

1 Maluf, N. An introduction to Microelectromechanical Systems Engineering. Artech House (2000).

2 Baumann, WH et al. Microelectronic sensor system for microphysiological application on living cells. Sensors and Actuators B55,77-89 (1999).

3 Winnips, CC. Drug delivery. Drug Discovery World Winter 2000/1 62-66.

4 Moore, GE. Cramming more components into integrated circuits. Electronics 38,114-116 (1965).

5 Canham, L and Aston, R. Will a chip every day keep the doctor away? Physics World 14(7) 27-31 (2001).

6 Buriak, JM. J.ChemSoc. Commun. 1051 (1999).

7 Berner, B & Dinh, SM. Electronically controlled drug delivery. CRC Press, Boca Raton, FL (1998).

8 Fraser, DM. Biosensors in the body: continuous in-vivo monitoring. pp258 Wiley (1997).

Other references

Canham, LT. Bioactive silicon structure formation via nanoetching techniques. Adv.Mater. 7,1033 (1995).

Canham, LT. Properties of porous silicon. IEE EMIS Datareview No 18 (IEE Publ. 1997).

Cowen, S and Legge, C. The 'lab on a chip' and its impact on drug discovery. Drug Discovery World Fall (2001) 51-56.

Evered, D and O'Connor, M. Silicon biochemistry. John Wiley & Sons (1986).

Kapur, R et al. Streamlining the drug discovery process by integrating miniaturisation, high throughput screening, high content screening and automation on the CellChip system. Biomedical Microdevices 2, 99 – 109 (1999).

The Next Small Thing: An introduction to nanotechnology. Merrill Lynch Report RC 30224705. Sept 2001.

Website

International Technology Roadmap for Semiconductors: www.itrs.net/ntrs/publntrs.nsf