Future work

Studies with the capsule in mice and rats have been promising – short-term normoglcaemia has been shown – and are still ongoing. Desai's group are working with the Department of Cell Transplantation at the University of Illinois, and their next step will be to take the technology into studies with larger animals to determine the parameters that will need to be scaled up to adapt the capsule for humans. 'One of the crucial aspects is to find out how many cells will be needed to have a therapeutically effective dose of insulin,' explains Desai. 'So, you don't want to have overexpression of insulin, just as much as you wouldn't want underexpression. But, to some extent the cells will self-regulate.'

The capsule technology could also be applied to other therapies, and Desai has just begun working with others to develop a capsule that contains neurosecretory cells that could potentially produce therapeutic agents for use in Alzheimer's and Parkinson's diseases.

Reference

1 Leoni, L. and Desai, T.A. (2001) Nanoporous biocapsules for the encapsulation of insulinoma cells: biotransport and biocompatibility. *IEEE Trans. Biomed. Eng.* 48, 1335–1341

2 Desai, T.A. *et al.* (2000) Micromachined interfaces: new approaches in cell immunoisolation and biomolecular separation. *Biomol. Eng.* 17, 23–36

See the forthcoming critical review of stem cell technologies in *Drug Discovery Today* that provides additional information on potential new therapies for diabetes.

Smart bandages diagnose wound infection

Jo Whelan, Freelance writer

Silicon-based biosensors that change colour in the presence of pathogenic bacteria could be incorporated into 'smart' bandages for dressing wounds. Researchers at the University of Rochester (Rochester, NY, USA) have developed a sensor, which they say is the first advance in the identification of Gram-negative bacteria since Hans Gram developed his famous stain in 1884.

Many potentially dangerous wound infections are caused by Gram-negative bacteria, which carry a lipopolysaccharide known as endotoxin on their cell membrane. Such infections can lead to sepsis, a potentially fatal systemic response that is usually triggered by the presence of endotoxin and can result in dangerously low blood pressure and organ failure. To diagnose the presence of Gram-negative bacteria, clinicians must still rely on the Gram test. This involves making a smear slide of a sample from the wound, performing staining and decolorization procedures and examining the slide under a microscope. This is time-consuming and error-prone, as the result is dependent both on the quality of the slide and the subjective judgement of the person examining it.

Figure 1. A porous silicon microcavity resonator. The device is used as a biosensor to detect Gram-negative bacteria (shown in the background). Figure kindly supplied by Elizabeth Lamarck, University of Rochester (Rochester, NY, USA).

Luminescence

'It's amazing that we're still using a procedure that's effectively out of the Stone Age,' says Ben Miller of Rochester's Department of Chemistry. Miller, Philippe Fauchet and colleagues have developed a silicon-based biosensor that detects lipid A, a component of the bacterial endotoxin lipopolysaccharide [1]. The technology uses porous silicon, formed from etching millions of tiny holes into a silicon wafer. This is an ideal material for biosensors, first because the porous structure provide a large surface area for contact with target molecules, and second because the nanocrystals present in the structure are photoluminescent in the visible range of the spectrum at room temperature. To narrow the luminescence to a useful bandwidth, the sensor material can be sandwiched between further layers of porous silicon that allow only selected wavelengths to escape. These devices are known as porous silicon microcavity resonators and are only a few microns thick (Fig. 1) [2]. They have already been used successfully in biosensors to detect

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specific DNA sequences and proteins [2,3].

Lipid A was chosen as the target for the sensor because it is highly conserved within the variation in endotoxin composition that is found across different bacterial species. The Rochester team designed and synthesized an organic receptor molecule, known as tertryptophan *ter*-cyclo pentane (TWTCP) [1], which binds specifically to disphosphoryl lipid A in water via a precisely shaped molecular cavity. An amine was added as a blocker to prevent all the TWTCP binding sites from binding to the silicon substrate. Binding between TWTCP and lipid A caused a change in the refractive index of the silicon, producing an 8 nm red shift in the wavelength of its photoluminescence peak.

The sensor was then exposed to solutions of lysed Gram-positive and Gram-negative bacteria, respectively. Gram-positive cultures produced no detectable red shift, but each of three different Gram-negative species produced a shift of 3–4 nm [1]. This cannot be detected by eye and must be read electronically. 'At the moment we can detect about 1.7 μg of bacteria, but that can be improved,' says Fauchet, who is Chair of Rochester's Department of Electrical and Computer Engineering. 'Our work with DNA and proteins shows that these sensors are at least as sensitive as the other technologies available.'

Differentiating between species

The next step will be to devise receptor molecules that will differentiate between different organisms. This is currently only possible by growing bacterial cultures, which take between 24 and 72 hours to produce a result. The team has already selected targets that are specific to pathogenic listeria, salmonella and *Escherichia coli* species. Ultimately, they hope to be able to selectively detect antibiotic-resistant strains within species. 'That will be extremely challenging,' Miller admits, 'but we think we can do it.' Arrays of sensors could be incorporated into a 'smart bandage' that could provide early warning of serious infection without the need for invasive wound sampling and time-consuming cultures. The sensors themselves are inexpensive to produce, although the reader is currently bulky and expensive. However, Fauchet is confident that a cheap, convenient device could be developed easily. It could also be possible to refine the sensor so that the colour change is visible to the naked eye.

'This type of technology could give same-day answers if you need to identify the presence of particular bacterial species,' says Phillip Mannion, Consultant Medical Microbiologist at the Countess of Chester Hospital (Chester, UK). 'However, it is important to distinguish between wound colonization and wound infection, particularly in chronic wounds like pressure sores, where Gram-negative bacteria commonly colonize the wound without any harm to the patient.'

Dressings containing the sensors will have to be evaluated in clinical trials, and no timetable for this work has yet been set. However, a major pharmaceutical company has expressed interest in the technology. 'Clinical trials would have to show quicker diagnosis time for infection, thereby allowing earlier intervention with relevant therapies,' comments Mannion.

References

1 Chan, S. *et al.* Identification of Gram-negative bacteria using nanoscale silicon microcavities. *J. Amer. Chem. Soc.* (in press)

2 Chan, S. *et al.* (2001) Nanoscale silicon microcavities for biosensing. *Mater. Sci. Eng.* C15, 277–282

3 Chan, S. *et al.* (2001) Nanoscale silicon microcavity optical sensors for biological applications. *Mater. Res. Soc. Symp. Proc.* 638, F10.4.1–F10.4.6