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Self-regulating insulin bioreactors for diabetes

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An implantable capsule that could self-regulate its own production of insulin in response to a patient's blood-glucose level has been developed as a promising alternative to current diabetes therapies [1]. The capsule boasts two advantages: first, the ability to continuously produce insulin according to demand; and second, being designed to circumvent immune rejection. Tejal Desai, a biomedical engineer at the University of Illinois (Chicago, IL, USA), received funding from the National Science Foundation (Arlington, VA, USA) to develop the innovative sustained delivery device, which is currently being tested in small animals.

As with all protein drugs, insulin cannot be administered orally because it will be rapidly degraded in the stomach. Therefore, the only option for diabetics is to endure frequent injections of insulin, which is painful and hinders drug compliance.

The capsule developed by Desai is ~2 × 4 mm in size and has been precision engineered in silicon using photolithographic technology, a technique commonly used in the manufacture of microchips because it can create large batches of small structures reproducibly. To prevent rejection of the capsule by the body's immune system, the structure of the capsule incorporates a so-called 'immunoisolation' membrane made of silicon that has been surface micromachined to form several thousand pores each as small as 10 nm in diameter (for a recent review on microfabrication technology see ref. 2). This membrane acts as a filter to allow glucose, oxygen and nutrients into the capsule to maintain the cells, while preventing the influx of antibodies (Fig. 1).

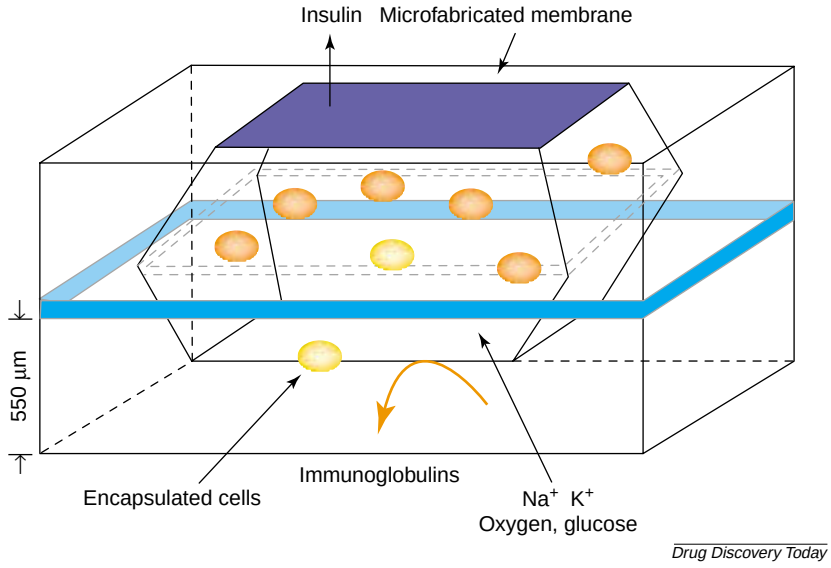

Figure 1. Diagram of basic microfabricated immunoisolation biocapsule concept. Reproduced, with permission, from Ref. 2.

Bioreactor

The capsule has been described by Desai as a kind of mini-bioreactor because it contains insulin-secreting primary rat cells from the pancreas or mouse insulinoma cells. Glucose from the body can pass into the capsule via the nanopores and trigger the production of insulin by the implanted cells. Insulin then diffuses out of the capsule and into the patient's bloodstream, and is able to self-regulate its further production by the capsule by negative feedback inhibition, that is, by reducing the blood-glucose level of the patient.

The ability of the capsule to continuously manufacture insulin on demand would eliminate the 'burst' of drug release that is commonly seen with other delivery devices. Furthermore, after implantation either intraperitoneally or subcutaneously in the arm, the implant could be used to administer insulin for long periods of time, which would be a welcome alternative to having frequent, painful injections for diabetes patients. 'If primary cells are used,' Desai explains, 'then in a truly optimal case the implants could possibly last indefinitely, and if not indefinitely they could certainly last for several years.' Desai is currently studying capsules that were implanted intraperitoneally, but aims to extend this to look at subcutaneous implantation. 'There is definitely a trade-off between ease of implantation and efficacy, that is, it is easier to implant the capsule in the arm, but it is more effective intraperitoneally.'

The cells used in the capsule can originate from animal, as well as human sources, which Desai says avoids the problems associated with the shortage of human organ donors.

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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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