to a cytosolic receptor protein, FKBP12. FKBP is upregulated in response to vascular injury providing a unique targeting mechanism preferentially directing Sirolimus to injured cells.

Cordis says that, because Sirolimus inhibits the cell cycle at the early-stage G1–S checkpoint, it produces a safe cytostatic response, whereas inhibition of the cell cycle at later points will induce cell death and mutational changes. However, Fearnot says that, 'All drugs have the potential to be cytotoxic. It is the dose used that is important.'

Fearnot believes that paclitaxel shifts the equilibrium so that tubulin does not cycle between the insoluble and soluble forms because, for cells to divide, tubulin needs to be in the soluble form. Meanwhile, actinomycin D is a potent antibiotic that binds with DNA to inhibit RNA-polymerase-mediated transcription. It also causes single-strand breaks in DNA.

There are concerns that all of these drug-eluting stents could limit the growth of a layer of cells that is necessary to cover the stent and prevent bare metal from coming into contact with the blood, an event that could lead to clot formation. 'Another danger is that cells in the vessel wall could stop dividing resulting in vessel wall disruption and thrombus,' warns Karl Karsch, Chairman of Cardiology, University of Bristol (Bristol, UK). He adds that it could also be difficult to control the concentration of drug because the concentration in calcified vessels will be completely different from other vessels.

Future prospects

Stents could eventually be developed to deliver gene therapies and cholesterol-lowering agents, such as statins, to the vessel wall. But some predict that the stent's heyday will be short lived. 'My opinion is sophisticated molecular therapy, delivering genes and cellular modifiers in a more deliberate way, will be the future. In 10 years, mechanical interventions like stents are likely to be defunct,' says Karsch.

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Drug delivery through the keyhole

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A new biomaterial delivery system has been developed that could create novel opportunities for targeted drug delivery. The Celltran™ delivery system, developed by BioDelivery Systems (Portland, OR, USA), consists of a delivery instrument and proprietary gel matrix, which aim to solve the problems associated with current methods of delivering biomaterials and other surgical materials.

Existing technologies

Current methods for delivering biomaterials generally use needle syringes, but this has several drawbacks arising from the simple mechanics of injection. Turbulence, shear forces and the high pressure that is created as material is forced from the barrel through the needle can destroy a significant percentage of living cells in a formulation. When the implantation technique that was found to be optimal was used, as many as half of the implanted cells were not viable one hour after implantation[1]. Viabilities of 55–85% were recently reported following percutaneous testicular sperm aspiration through a 20 gauge needle[2]. It is also difficult to administer highly viscous solutions using a needle syringe. Additionally, problems can occur at the site of delivery, where the high pressure created during an injection can cause embolism[3] or leakage to other sites[3,4].

An alternative to needle syringe application is to place the biomaterial directly on the target site using invasive surgery. However, this has the usual problems associated with a more invasive medical procedure.

'When you start using it [a needle syringe] for purposes it wasn't designed for, that's when you run into problems,' commented Carl Wilcox, President of BioDelivery Systems. 'The needle syringe design delivers material to a site without relieving the delivery pressure… [and can] destroy up to 50% of cellular or

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biological material. We tested three or four formulations that showed that our system allowed cell survival…in excess of 90%,' he said.

Celltran system

The Celltran system is designed as an improvement over existing biomaterial and living-cell delivery methods by being easier to use, preserving more of the material it delivers, targeting the delivery and reducing migration, while providing nourishment and support to the biological material being delivered. The instrument itself possesses a rotating delivery mechanism, which relieves delivery pressures and generates minimal turbulence in the injector body. The gel matrix can be custom-made to suit specified bioabsorbability and solidification requirements.

The whole system is disposable and one model has been designed to fit any industry standard endoscopic instrument. It is designed to be minimally invasive, which enables the technique to take advantage of existing keyhole surgery technology, such as the option for the operator to have visual feedback[5]. The greater accuracy with which materials can be placed should reduce the risk of an embolism being created and material leaking into adjacent tissue.

Supporting studies

Shelley Winn, Gel Matrix Research Director at BioDelivery Systems and Associate Professor of Surgery at Oregon Health Sciences University (Portland, OR, USA), said: 'We have completed several studies in tissue-culture systems that show conclusively an enhancement of survival/functionality following delivery through a Celltran prototype, compared with delivery with needle–syringe technology.' They are planning to publish this supporting data in 2002. Although the direct details of the Celltran system are currently unavailable while the patent is still pending, previous studies have been published using early iterations of some of the components. Much of the supporting studies, to date, have been used in experimental bone regeneration models. These formulations must act as a substrate to provide a site for attachment and differentiation of host pluripotent (stem) cells. In addition, the formulations should be convenient for the surgeon, and should exhibit an ability to localize, position and sustain combinations of cueing molecules, such as growth factors and morphogens (bone morphogenetic factors), DNA plasmids or other gene transfer vehicles, and cells at the wound site.

Winn and his colleagues developed a tissue-engineered bone biomimetic device to regenerate skull defects in rats[6]. The biomimetic composite of a porous resorbable scaffold containing a human-derived osteoprecursor cell line (OPC1; Ref. 7) distributed within a gel matrix regenerated more host bone at four weeks than the group receiving the scaffold alone. The gel matrix is a crucial component to distribute and maintain the osteoblast precursor cells (OPCs) within the bone biomimetic device. Studies are currently under way to evaluate the potential efficacy of using modified formulations of an injectable gel matrix without the porous resorbable scaffold.

The prototype scaffold, composed of type I collagen (PLC)–human osteoblast precursor cells (OPCs) and rhBMP-2, was shown to regenerate more new bone in a rat calvarial critical-sized defect than three other devices: porous poly(D,L-lactide) and PLC; PLC and OPC at 2×10^5 (PLC–OPCs); and PLC and 50 g of rhBMP-2 (Ref. 6).

Future applications

The Celltran system will initially be used to deliver highly viscous, existing surgical materials. When approved, Celltran will also be used to deliver biomaterials for bone, cartilage and tissue regeneration, and the placement of growth factors, DNA and other biological materials. Because the system is designed to deliver such a wide range of materials there is a good possibility that it could be used to acutely deliver drugs to the body.

'Without a doubt, drug delivery is one of the major areas that will have an impact on material and cell delivery systems,' commented W. Mark Saltzman, Professor of Chemical Engineering at Cornell University (Ithaca, NY, USA). In work just published[8], combining cell transplantation with a drug-delivery system 'greatly enhanced the effectiveness of transplantation', he said.

'Drug delivery opportunities will be addressed according to the market,' says Wilcox. However, they are just at the 'preliminary stages of drug delivery'. The company already have several studies underway for strategic partners, involving their biomaterial delivery requirements, which he characterizes as 'very promising'. 'There is also a biomaterial company, that has had many problems delivering a liquid bone compound, that is interested in our technology,' he says. 'Right now I'm not aware of many drugs being delivered using minimally invasive techniques. I don't think that's because nobody wants to do it… but rather, because there hasn't been a system designed to do it.'

Oncology is another example of an application that could realize benefits from the system. 'For any drug that would need to be delivered in an acute surgical setting into a specific area of the body, we would have the potential of doing a better job than other instruments are able to do.'

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