non-fouling surfaces. How resistant to protein adsorption can such surfaces be made? Why are they resistant to protein adsorption? How long can they remain resistant to protein fouling? These are the questions that drive this area of research. Many of the materials currently being explored are surface-modified polyethylene glycols (PEGs).

Another recent example uses radio frequency-plasma deposition of tetraethyleneglycol dimethylether onto the surface of materials such as Teflon™ and polyethylene. Untreated Teflon and polyethylene adsorb a layer of protein to an extent of 93.6 ng cm^{-2} and 91.0 ng cm^{-2}, respectively. By comparison, the corresponding tetraglyme-treated materials both adsorb a layer of protein ~1.7 ng cm^{-2} thick. However, these *in vitro* studies give no indication as to whether these surfaces will turn off the foreign body reaction, and they certainly do not transmit signals that promote normal healing.

Promoting wound healing

Several materials have been discovered, many fortuitously, that promote healing in a way that is more similar to normal wound repair and less toward collagenous encapsulation. So far, most of these materials have only shown good integration into bone. However, the healing process in bone, as in other tissues, begins with macrophages, and so these materials could serve as good starting points.

Titanium is one example; untreated titanium heals in bone, but there is a thin (50–200 Å) organic layer separating the bone and metal, and no bonding between them. By comparison, titanium treated with a strong base and high temperature fuses to the bone. Other materials that promote normal healing include tyrosine polycarbonates and hydroxyapatite. Hydroxyapatite, a form of calcium phosphate, comprises the mineral portion of bone and, therefore, is less prone to attack by the immune system. However, as a material it is not applicable to the fabrication of all medical devices.

Porous materials

Biocompatible porous materials have also been explored for their ability to promote normal healing. When implanted, most were encapsulated by avascular, collagenous sacs, the classic foreign body reaction. However, some of these materials promoted healing that was closer to normal, with reduced collagen formation, an open structure to the collagen and blood vessels in close proximity to the implanted membrane.

The materials that promoted this special healing response had several characteristics in common, including pores of 5–15 μm, interconnectivity between the pores and the absence of expanses of flat surface onto which the inflammatory cells could spread. This healing reaction was seen with several different kinds of materials as long as they possessed the listed characteristics, independent of material type. Similarly, it has been found that fine, electrostatically spun fibers with diameters <5 μm generate little or no collagen encapsulation.

Matricellular proteins

The matricellular proteins that are always found in healing wounds are currently being explored for their potential uses in biomaterial research. These proteins have a role in the foreign body reaction and in normal wound healing; they effectively turn healing on and off. Included in this class of proteins are osteopontin, thrombospondin-2 (TSP-2) and osteonectin.

Osteopontin downregulates inducible nitrogen oxide (NO) synthase and reduces NO in macrophages and other cells. It has been shown to enhance cell survival, inhibit calcification and calm inflammation. A study of titanium coated with osteopontin suggests that it can enhance healing in bone.

TSP-2 is a member of a family of secreted glycoproteins that is upregulated in wounds. When silicone elastomer implants were placed in TSP-2 knockout mice and examined after four weeks, they were found to have a higher blood-vessel density in their vicinity and an open, unoriented collagen structure surrounding the implant. Osteonectin binds to many other biological compounds, including hydroxyapatite, collagen, vitronectin and TSP-2. It has also been associated with wound healing and angiogenic activity.

The future

The real question regarding matricellular proteins is whether their properties can be applied successfully to the surfaces of medical devices. What strategies might be used to immobilize them in a precise manner? Will one of these proteins be sufficient, or will several be required to promote normal wound healing around an implanted device? Can issues of cost, stability and sterilizability be addressed?

In the near future, researchers at the interface of biology, in particular wound healing, and biomaterials research will be faced with these challenges. Over time, ideas from other areas will also make contributions to this area, such as self-assembly, supramolecular structure, genomics and nanofabrication. In the meantime, the complexity of the problem will push the skills of surface scientists and bioengineers to the limits.

1 Ratner, B.D. (2002) Reducing capsular thickness and enhancing angiogenesis around implant drug release systems. *J. Control. Release* 78, 211–218

A novel nasal nicotine formulation for smoking cessation

Smoking is the most prevalent preventable cause of death in modern society. It causes one in five deaths in the UK and accounts for nearly half a million deaths in the USA every year. Despite this well-known fact, it proves to be difficult for a smoker to quit. When smoking, a dose of nicotine is rapidly delivered to the nicotine receptors in the brain, dopamine levels increase and a pleasurable

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sensation results. This quickly develops into physiological and psychological addiction, strongly reinforced by unpleasant withdrawal symptoms should the smoker attempt to cease smoking. At least 90% of smokers are to some extent dependent on nicotine, 75% are moderately to strongly dependent and the majority of the latter group continue smoking despite attempts to stop.

The most widely used treatment for smoking cessation is nicotine replacement therapy (NRT). NRT treatments are available in many dosage forms, including chewing gum, sublingual tablets, adhesive transdermal patches, nasal sprays and oral mucosal inhalers. These NRT formulations either give a rapid, short-lived plasma level peak of nicotine (i.e. nasal spray), or a slow onset with prolonged, sustained plasma nicotine levels (i.e. chewing gum and transdermal patches). None of the current NRT dosage forms provide the smoker with both the high and rapid peak arterial levels of nicotine obtained from a puff on a cigarette, as well as a prolonged, sustained level of nicotine to prevent cravings. A transdermal patch will provide a prolonged sustained level of nicotine that decreases cravings to some extent, but the patient never gets the immediate rush they receive when puffing on a cigarette. A nicotine nasal spray provides rapid nicotine absorption, but when used as the only NRT regimen the suggested dosage is 8–40 times per day to stave off nicotine cravings. In a recent study in patients who had previously failed nicotine patch therapy, six-month abstinence rates were extremely low, essentially 0% for the nasal spray. In general, the currently available NRT regimens are not entirely successful in achieving smoking cessation.

An improved NRT formulation

An NRT formulation that combines the two approaches, an initial rapid pulse of nicotine and a sustained release effect, could have significant advantages over current formulations. Cheng and coworkers have recently described the development of such an approach based on a nicotine–AMBERLITE® (Rohm & Haas Company; http://www.rohmhaas.com) resin complex combined with unbound nicotine in a nasal formulation [2]. Nicotine–AMBERLITE-complex powders were prepared and shown to exhibit sustained release of nicotine *in vitro*. One of these powders was chosen for further study. The powder was combined with unbound nicotine to produce a formulation that exhibited a quick pulsatile release followed by a sustained release of nicotine in a sheep animal model.

There are several AMBERLITE polymers that are sulfonated co-polymers of styrene and divinylbenzene. They are insoluble, strongly acidic, cationic exchange resins that are supplied commercially in the sodium form. In the present study, AMBERLITE IRP69 was the polymer of choice because it is suitable for use in pharmaceutical applications, both as an active ingredient and as a carrier for basic drugs. Neutral nicotine is a small basic compound with pKa values of 3.2 and 8.0. Higher loadings were achieved by using nicotine hydrogen tartrate in place of neutral nicotine in the preparation of the nicotine–AMBERLITE-complex powders. The powders were prepared by simply suspending the AMBERLITE resin in aqueous solutions of nicotine hydrogen tartrate and filtering off the supernatant. The loading of nicotine on the resultant powders was determined by assaying the free non-bound nicotine at 260 nm using a diode array detector.

Nicotine–AMBERLITE powder complexes were tested for their *in vitro* release rates. Nicotine–AMBERLITE powder complexes with loadings of 22, 36 and 56% w/w nicotine were compared to a control solution of aqueous nicotine hydrogen tartrate in a flow cell with a cellulose nitrate membrane. The nicotine hydrogen tartrate control solution showed fast diffusion (less than 10 min to completion) into the diffusion cell indicating that no interaction of drug took place with the diffusion membrane or the silicone tubing. The release profiles for the nicotine also show that the higher the drug loading, the faster the rate of release of nicotine. At 30 min, only ~20% of the nicotine was released from the 22% w/w loaded resin, whereas 60% of the nicotine was released from the resin loaded with 56% w/w nicotine.

The powders loaded with 56% w/w nicotine were chosen for production of formulations used for *in vivo* studies in sheep. Sheep make an ideal model for nasal delivery of drugs because of their large nares, the anatomical similarity to the human nasal cavity in terms of nasal cavity surface area per kg body weight, the accessibility of veins for cannulation and their mild temperament under experimental conditions. It has also been demonstrated that results obtained in the sheep model correlate well to data obtained in humans.

Nicotine–AMBERLITE complex powders with 56% w/w nicotine have the maximum achievable loading of bound nicotine. For the *in vivo* sheep studies, formulations with varying amounts of unbound and bound nicotine were prepared. The nicotine–AMBERLITE-complex powder was used directly as formulation F2, with 100% bound drug. The powder was combined with various amounts of unbound nicotine hydrogen tartrate to produce formulations with 50% bound drug (F3), 80% bound drug (F4) and 67% bound drug (F5). An additional dosage form with 80% bound drug and twice the total dose of nicotine was also administered by doubling the amount of F4, and this dosage form was designated F6. An aqueous solution of nicotine hydrogen tartrate (F1) was administered as a control.

Results of studies in sheep

The formulations listed above were administered to sheep. The nasal liquid dose (F1) and nasal powder formulations (F2–F6) were divided equally between

both nostrils and administered via a nasal spray device and tracheal tubes containing the pre-weighed powder dose, respectively. The study was performed as a six-way crossover study in six female sheep with a minimum washout period of three days. Serial blood samples were collected at 0, 1, 3, 5, 10, 15, 30, 60, 90, 120, 150, 180, 240 and 300 min post dose and analyzed by a GC–MS assay. As expected, the absorption of nicotine from the control solution was rapid with a T_{max} of 2.3 min and a C_{max} of ~93.1 ng ml^{-1}. AMBERLITE formulations provided sustained plasma levels after nasal administration to the sheep, and varying the amount of unbound nicotine in the formulation had an effect on the timing of the peak plasma level. Formulations F3 and F5, with 50% and 67% bound drug, respectively, exhibited T_{max} values of 16.7 and 15.8 min, while formulation F2 with 100% bound drug exhibited a T_{max} of 20 min. The C_{max} also varied depending on the amount of unbound drug; formulations F2, F3, F4, F5 and F6 (double the dose of nicotine) showed C_{max} values of 22.6, 46.3, 42.3, 64.7 and 118.3 ng ml^{-1}, respectively. Overall, the combination formulations F3–F6 provided both a relatively rapid onset of peak plasma level nicotine followed by a prolonged sustained plasma level. From these data, the authors deduce that an optimized formulation to provide the preferred profile would have 35–40% unbound nicotine with the remainder of the dose bound to resin in the formulation.

This study demonstrates preliminary steps toward a nasal nicotine formulation capable of providing an initial rapid release and absorption of nicotine, followed by sustained release and controlled absorption. Some optimization is required; in particular the absorption of unbound nicotine from the formulation (T_{max} ca. 15 min) is not as rapid as that obtained from a puff on a cigarette (T_{max} <1 min). However, the pulse effect has the potential to provide an initial rapid peak in plasma nicotine levels that should give the described buzz effect of smoking a cigarette, and the sustained release should provide a high enough plasma level of nicotine to stave off nicotine cravings. Once optimized, this could prove to be a much better NRT regimen than those that are currently available. There should be interest in any therapy that could decrease such a prevalent, preventable cause of death.

2 Cheng, Y-H. et al. (2002) Development of a novel nasal nicotine formulation comprising an optimal pulsatile and sustained plasma nicotine profile for smoking cessation. *J. Control. Release* 79, 243–254

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