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Holy Grail of drug delivery caught using novel fishnet technology

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A novel controlled-release technology could revolutionize the delivery of protein drugs for use in cancer and many other diseases. InfiMed Therapeutics (Cambridge, MA, USA) has recently been awarded a US patent[1] that protects its Improved Formulation Entity (IFE™) technology platform for incorporating proteins and peptides into fishnet-like hydrogel polymers, which can be administered via several routes. Until now, developing a system that could deliver large, labile protein-drugs in a sustained, controlled manner was thought to be an impossible task.

Many protein drugs (such as insulin) are degraded rapidly by the stomach and have to be administered via frequent injections. Existing methods of protein delivery often cause a 'burst' of drug release and associated unpleasant side-effects, which reduces patient compliance and treatment efficacy, and wastes expensive protein drugs. InfiMed has focused on the delivery of major protein-drug candidates such as interferon, human growth hormone (hGH) and erythropoietin. The company will be embarking on Phase I clinical trials of a sustained-release hGH product in the near future and hopes to be in Phase III testing by the end of 2001.

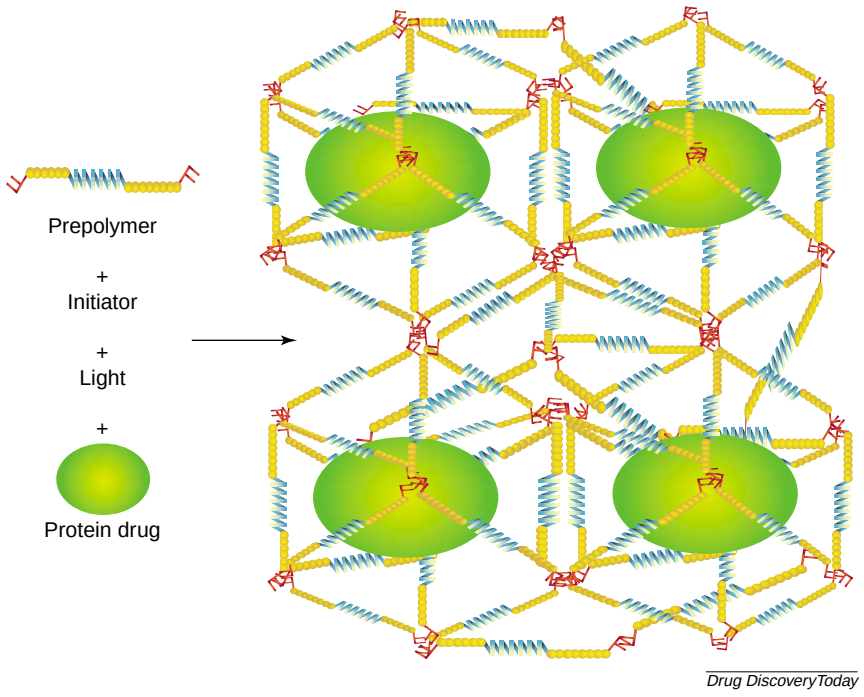

Figure 1. InfiMed's Improved Formulation Entity (IFE™) hydrogel technology: non-toxic hydrogel prepolymers consisting of a polyethylene glycol (PEG) backbone with biodegradable linking groups are mixed with the protein drug and photopolymerized to form a unique fishnet-like hydrogel structure with the protein drug uniformly encaptured within the 3D hydrogel microparticle.

The technology

The IFE technology uses water-soluble, non-toxic hydrogel prepolymers consisting of a polyethylene glycol (PEG) backbone with biodegradable linking groups, such as α-hydroxy acid, and acrylate termini at each end. An aqueous solution consisting of these prepolymers and a bioactive material, such as a protein drug, is photopolymerized to form a unique fishnet-like hydrogel structure with the protein drug uniformly encaptured within the 3D microparticle (Fig. 1)[2].

Once inside the body, these small microparticles (approximately the diameter of a human hair) degrade by hydrolysis of the α-hydroxy-acid linkers and release the protein drug. The microparticles then further degrade into water-soluble products that are excreted by the kidneys; 'The whole chemistry is very safe', says Stephen Rowe, President and CEO of InfiMed. Indeed, the safety and efficacy of the hydrogel technology has already been proven in studies carried out by Focal (Lexington, MA, USA; co-founded by Rowe and his colleague Jeffrey Hubbell) that demonstrated its application in wound healing, by both the formation of a sealant-barrier on the skin and the localized release of urokinase and tissue plasminogen-activator[3].

Rowe explains that: 'In general, no one has really come up with something that has found any significant market acceptance in terms of a sustained-release protein formulation. That is not the case with peptide drugs: polylactic acid (PLA) formulations can work effectively for

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3–4 months. In essence, I think we have something that is effective for protein drugs for up to a month, or perhaps more, and for peptide drugs we can achieve efficacy for ~3–6 months because peptides are inherently more stable at body temperature.' He continues: 'What is nice about the system is that we can ''dial in'' to the release profile by changing the percentage of the polymer we have within the microsphere, or the number of degradable groups, to give us exquisite control over the release profile.'

Rowe anticipates that this technology can be used to eliminate the burst often created by administration of protein drugs such as hGH and interferon (Fig. 2). This is possible because of the unique nature of the fishnet-like structure, which means that the protein drug is not released until the hydrogel starts to degrade. By contrast, PLA-microsphere drug delivery systems tend to be porous so that on administration to a tissue, the microspheres act like a sponge and their contents enter the body rapidly and create a burst. Usually, administering large quantities of protein exaggerates the problem of burst, but because hydrogel microspheres are not as porous as other delivery vehicles, relatively high protein-loading can potentially be achieved. Moreover, this technology does not involve binding of the protein to a delivery vehicle, therefore, retaining the integrity of the protein.

Claudio Mapelli (Principal Scientist, Bristol-Myers Squibb, Princeton, NJ, USA), believes that: 'The sustained, controlled drug release that seems possible with IFE could certainly represent a major advancement in the delivery of peptide and protein biologics. Effectively, this could position IFE very competitively relative to other drug depot formulation approaches such as subcutaneous implants.'

The sustained release of several proteins using the IFE technology has been proven by research in animal models.

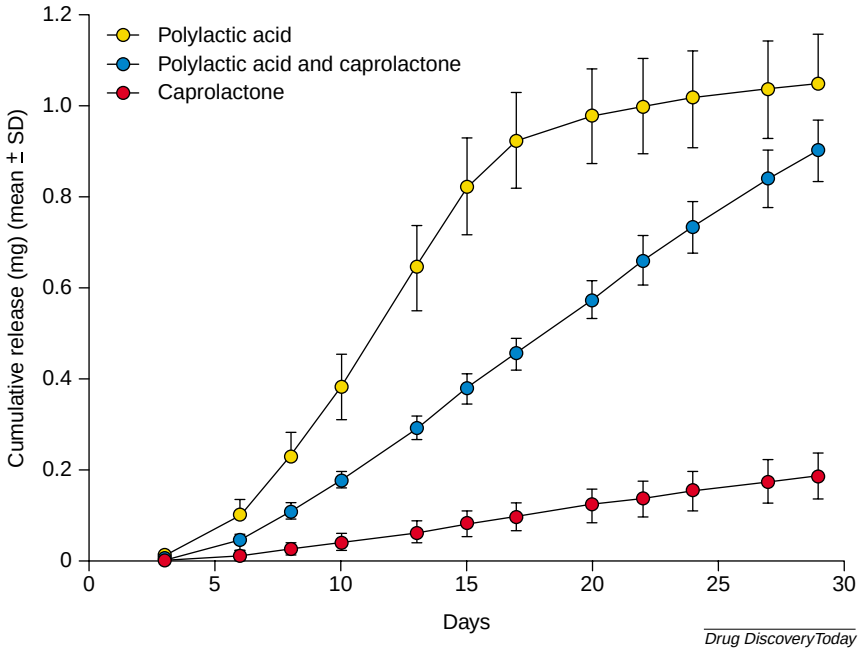

Figure 2. Release kinetics showing the efficacy of InfiMed's Improved Formulation Entity (IFE™) hydrogel technology. *In vitro* release of growth hormone was measured by size-exclusion HPLC from hydrogel microspheres composed of either polylactic acid links, caprolactone links or a blend of the two polymers. The chart shows that by altering the polymer composition of the microspheres, a different release curve can be achieved, and that there is a delay in release of the drug, rather than the burst that is often seen with other delivery systems.

In hypophysectomized rats, administration of hGH by controlled release from a hydrogel implant was shown to be as effective as daily subcutaneous injections at inducing growth of the animals, confirming previous data obtained with bovine somatotropin[1]. Furthermore, studies in diabetic rats using a subcutaneous hydrogel implant to deliver insulin significantly lowered blood glucose levels, thus demonstrating that insulin was released in an active form[1]. As Mapelli points out, 'One of the biggest problems in the clinical management of diabetes is that current intravenous insulin injections cause bursts of drug release and unwanted fluctuations in glucose levels. The controlled release of insulin produced by the IFE approach leads to steadier, as well as lower, blood glucose levels. Now, the critical question is whether these results can be reproduced in humans.'

Delivering the goods

Protein delivery using IFE technology can potentially be achieved via several routes. If injected subcutaneously, the protein will be released in a controlled manner at the site of injection and will subsequently enter the systemic circulation. Intravenous administration could prove particularly effective for cancer treatment; the blood flow within tumours is often slow as a result of leaky vasculature and, therefore, it is hypothesized that the microparticles could become lodged and provide a means of administering the drug directly within the tumour. Microparticles could also be shaped to fit a particular body cavity, providing a depot from which the controlled release of a drug can be achieved. There is also the potential to deliver drugs orally, intranasally and via inhalation, using either freeze-dried microparticles or microparticles in solution.

Mapelli comments: 'A major advantage of IFE – although more data will be needed to demonstrate it – is the scope and versatility of the routes of administration it can utilize', he continues: 'I think that the IFE platform could have an even bigger impact on how drug biologics are developed and delivered if it could allow, at least in a few therapeutically significant cases, oral dosing of protein or peptide drugs.'

Future strategies

InfiMed now plans to launch a daily liquid formulation of hGH, Infitropin-AQ™, on the US market in collaboration with Grandis Biotech GmbH (Novartis, Freiburg, Germany), and is developing its own sustained release version, Infitropin-CR™, for marketing in North America, which should enter clinical trials in the near future. InfiMed has an agreement with Grandis, under which Grandis will market Infitropin-CR in Europe. Furthermore, InfiMed is hoping to enter into corporate partnerships for the development of sustained-release forms of therapeutically and commercially successful protein drugs, such as erythropoietin, α- and β-interferon, and granulocyte-colony stimulating factor (G-CSF), in addition to generating products for its own development pipeline.

In the long term, future applications of IFE technology might include the tissue-specific targeting of proteins and improved delivery of novel drug candidates that arise from the recent advances with the Human Genome Project.

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References

1 Hubbell, J.A. *et al.* (2000) Biodegradable macromers for the controlled release of biologically active substances. US6,153,211
2 West, J.L. and Hubbell, J.A. (1995) Photopolymerized hydrogel materials for drug delivery applications. *React. Polym.* 25, 139–147
3 Hubbell, J.A. (1996) Hydrogel systems for barriers and local drug delivery in the control of wound healing. *J. Control. Release* 39, 305–313

Sixth sense could avoid the blood–brain barrier

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The first lead compound to come from a series of synthetic pheromones has shown promise in a pilot study for acute anxiety in women and is hoped to provide a new method of avoiding the problems associated with delivery across the blood–brain barrier. Pherin Pharmaceuticals (Mountain View, California, USA) have produced PH94B from a series of over 1000 patented 'vomeropherins', synthetic variants of naturally occurring pheromones that stimulate the vomeronasal organ (VNO).

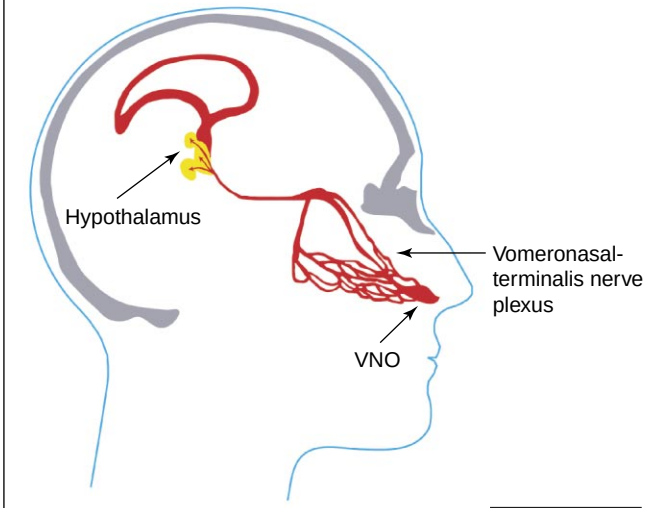

Figure 1. The vomeronasal organ (VNO)–hypothalamus pathway.

The VNO

The VNO is located in the nasal passages of most mammals and some reptiles and was first described in mammals in the early nineteenth century, when it was suspected to be a sensory organ[1]. In lower mamals, it is known to mediate sexual and reproductive behaviour in response to pheromone binding.

As recently as 1998, the human VNO has been described by some investigators as 'vestigial'[1]. However, there is substantial evidence to show that it can act as an additional sensory system – a 'sixth sense'[2]. The human VNO is a bilateral, tubular

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