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.

Acknowledgements

I would like to thank Stephen Rowe, Guy Gelardi and Claudio Mapelli for their help with this article.

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Sixth sense could avoid the blood–brain barrier

Clare Sansom, Freelance writer

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).

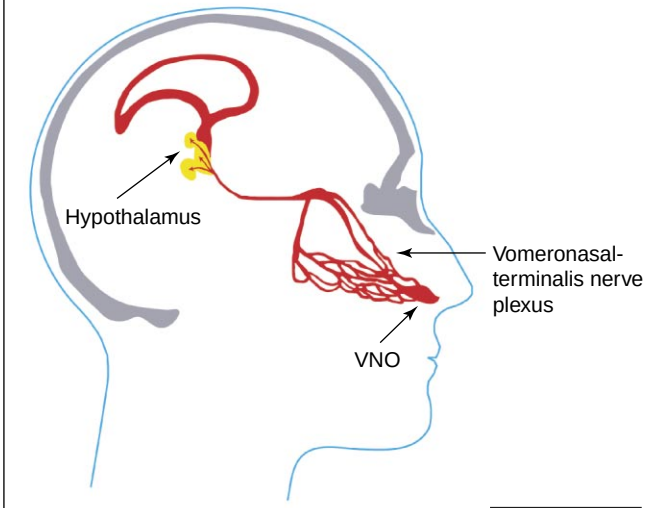

Figure 1. The vomeronasal organ (VNO)–hypothalamus pathway.

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

 PII: S1359-6446(01)01772-X

pit, approximately 1 cm long, which is located inside the nasal septum (Fig. 1). It is, however, distinct from the olfactory system as most of the compounds that stimulate the VNO have no odour, and it does not respond to many odorants.

Stimulation of receptors on the surface of the VNO by pheromones triggers an electrophysiological response, which transmits neural impulses to the hypothalamus. Kevin McCarthy, Senior Vice-President of Pherin, says: 'The VNO links the endocrine system to the nervous system via the hypothalamus. Synthetic compounds that stimulate the VNO might affect those emotions and physiological functions that are controlled by that area of the brain: from anxiety, aggression and fear to appetite and sexual motivation.'

While working at the University of Utah, Louis Monti-Bloch, now Vice-President of Research at Pherin, developed a multichannel system that delivers test substances into the VNO using a nasal spray and measures the voltage induced by depolarization of the receptor cells. The system delivers a continuous air stream containing discrete pulses of picogram quantities of pheromones and a plant oil vehicle to the VNO.

Many hundreds of synthetic pheromone analogues have now been tested using this system. Like natural pheromones, vomeropherins are species- and gender-specific. For example, the steroid vomeropherin pregna-4,20-diene-3,6-dione (PDD) is inactive in human females. In males, nasal delivery of nanomolar quantities of PDD results in a dose-dependent depolarization of the VNO receptors, followed by statistically significant decreases in cardiac and respiratory frequency and in the serum concentration of some hormones[3].

Testing in humans

As the effect of vomeropherins is species-dependent, they cannot be tested for efficacy in animal models. With the exception of toxicology tests, all preclinical research is carried out in human cell lines or using human volunteers. 'This is a blessing in disguise,' says McCarthy, 'as all the data we report will have been obtained from humans.'

Pherin has now reported encouraging results from a pilot study of their lead compound, PH94B, for acute anxiety disorders in women. This was a double-blind, placebo-controlled Institutional Review Board trial of female volunteers who scored highly on the Hamilton A diagnostic tool for anxiety and were not taking any other medication. All the women who received picomolar quantities of PH94B via a nasal spray showed a statistically significant reduction in their anxiety levels compared with controls, and no significant side effects were noted. Following these results, the FDA accepted Pherin's Investigational New Drug application for PH94B and Phase I clinical trial protocols are currently being designed, with trials expected to start before the end of 2001.

If PH94B and similar compounds prove effective in clinical trials, the VNO should offer several advantages as a drug delivery system. The vomeropherins are well tolerated, fast acting and active in very small quantities. Furthermore, this system affects the CNS through local stimulation of a sense organ and so compounds that are delivered in this way do not need to pass through the blood–brain barrier.

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Drugs with a magnetic attraction to tumours

Janet Fricker, Freelance writer

An innovative new approach that couples anti-cancer drugs to a carrier system containing iron that can be targeted by magnets to the tumour site is showing promise in both animal models[1] and Phase I/II clinical trials.

Many anticancer drugs are limited by their toxicity profile and by development of multiple drug resistance. FeRx (San Diego, CA, USA) believes that its proprietary Magnetic Targeted Carrier (MTC) technology makes chemotherapy more effective by increasing the drug concentration at the tumour site, while limiting the systemic drug concentration. Their studies have initially concentrated on delivering doxorubicin to hepatocellular carcinomas, this drug being one of the

1359-6446/01/$ – see front matter PII: S1359-6446(01)01771-8