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While BTG's president Sim Fass sees no need to circumvent Orphan Drug control of hGH before it expires in 1994, he suggests that oral delivery of hGH would improve not only the quality of the patient's life, but the quality of the drug as well. "Human growth hormone is released naturally in a pulsatile manner, with one large spike of drug occurring during the night," he says. "If we could use an oral system to administer that spike, less hGH would be needed, perhaps with a greater effect." And, he admits, with a unique marketing niche for BTG.

Fass says he looked at all the oral drug delivery options before selecting Enzytech, and he is still seeking other delivery systems. Asked what swayed him to Enzytech's side, he answered, "Their willingness to collaborate and their straightforward ability to discuss the science."

These views are echoed by Hubert Schoemaker, chairman and chief executive officer of Centocor, who liked what he saw so much that he bought into the company. "As Centocor gains sophistication in the uses of Fc fragments and complementarity determining regions (CDRs) of antibodies," says Schoemaker, "it will move into chronic care products for autoimmune and inflammatory diseases." Schoemaker sees oral delivery as the second punch in a one-two attack initiated through acute care or controlled release injectables.

Hold The Liver

Attempts to exploit a receptor-mediated pathway, initiated by Biotech Australia (Roseville, North South Wales, Australia) employ cyanocobalamin, vitamin B_{12}. Atypically in the drug delivery arena, the mechanism of uptake is fairly well understood. B_{12} binds to intrinsic factor in the stomach before binding receptors in the distal ileum. Biotech Australia's experiments with LHRH-B_{12}, and bovine serum albumin (BSA)-B_{12} conjugates demonstrated pharmacologic activity in mice by stimulating ovulation and producing anti-BSA antibodies respectively[5]. The company presented no data on the bioavailability of the conjugates and none to support transport via the cobalamin pathway. The mechanism by which the cobalamin dissociated from intrinsic factor in the low pH of the endocytic vesicle, the subsequent degradation of the binding protein and the method cobalamin becomes associated with transcobalamin before transport to the portal circulation are not known.

The main criticism of the system is its low uptake. B_{12} absorption peaks at 1-2 µg per day regardless of dose. Right now, this limits Biotech Australia's target peptides to those that require only nanomolar quantities to be effective–calcitonin analogues, LHRH agonists, and erythropoeitin (EPO). The company proposes to jump on the microsphere bandwagon—conjugating encapsulated proteins to vitamin B_{12}—to deliver larger proteins. While critics point out that successful chronic-treatment regimens would require a B_{12}-depleted diet to insure proper dosing, the company claims experimental animals responded without dietary restrictions.

Enhancers and Other Factors

Rapid transit times and high proteolytic activity combine with slow absorption kinetics to limit potential drug uptake. To facilitate absorption, "enhancers" are often added to formulations to stimulate uptake. Experimentation with surfactants designed to increase membrane permeability to hydrophilic molecules, are often disappointing because chronic use promotes irritation and and may leave the gut epithelium open to bacterial penetration. Since the gut daily reabsorbs approximately 18 grams of bile through both passive diffusion and active transport, bile salts continue to attract attention as transport mediators. Cholic acid derivatives with tosyl-, benzoyl-,or iodo- groups conjugated at the C3-OH position are considered likely candidates. Researchers are not only considering formulation possibilities, bile acids may also serve as carrier molecules in prodrugs. In this view metabolic clipping of the bile carrier from the protein would activate the drug.

Enhancers are contentious because little is known about the toxic effects of molecules used to disrupt physiological barriers. "We know that transporting toxins or pathogens is bad," says Randy Mrsny, head of Genentech's (So. San Francisco, CA) drug delivery/biology research, "we just don't know the threshold that produces a pathogenic state." Certain bile-derived enhancers may help open the gut membrane, increase absorption, and make oral systems more attractive once the data are in.

A biotech alternative to enhancers may develop from research on enteroinvasive bacterial surface proteins. Both *Salmonella* and *Shigella* penetrate epithelia through either inducible or constitutive expression of surface proteins. Once exposed to the epithelial layer of the gut, the proteins serve as a key—unlocking an endocytotic pathway. Mimicking these natural proteins may provide another mechanism for biotech drug delivery.

Colon Contacts

Jindrich Kopecek at the University of Utah (Salt Lake City) took a cue from enteroinvasive bacteria such as *Shigella* to launch another assault on peptide drug delivery—this time via the colon. Kopecek, amongst others, champions abandoning peptide drug delivery attempts in the small intestines. Advocates consider the colon a kinder, gentler environment for protein delivery, with reduced peptidase activity and longer transit time. But bacterial enzymatic activity, lack of carrier-mediated transport systems, and slower diffusion rates make the colon a formidable barrier.

Kopecek's strategy increases drug delivery time by forming mucoadhesive polymers that bind to the colon epithelium. Like *Shigella*, the polymers are coated with fucosylamine residues—sugar molecules implicated in mucosal binding. To get the molecules to the site, he employs hydro-gels, made of material similar to soft contact lenses. The hydro-gels are pH sensitive, protecting proteins from the acids of the stomach, and then swelling in the higher pH of the colon. This increases the permeability of the polymer, aiding in release of the drug. Bacterial enzymes in the colon biodegrade the cross-linked azobenzene molecules in the polymer, further facilitating drug release at the site.

While the delivery system appears clever, Kopecek readily admits that it is still at the level of basic science. Conducting the bioavailability studies which suggest efficiency of absorption are still in the offing.

A Breath of Fresh Air

After 15 years of research on drug de-

A VETERAN'S LESSONS

How could a dubious drug delivery scheme entice an international biopharmaceutical company to pay millions? How is it that so much of this wishful thinking is Ph.D driven—by researchers who maintain academic positions while pursuing a company "on the side." Here are four factors cited by one pharmaceutical executive with over twenty years in the business (who unsurprisingly asks to remain anonymous).

1. *Whatever is extremely complex, people think is easy.* Drug delivery is hard, peptide and protein delivery harder. The money attracts naive people whose own limited research leads them to believe everyone else must be stupid.

2. *Pharmaceutics is a derelict science.* Publications and research have not kept pace with scientific advances in the other fields. Few academics in this area have their work recognized by membership in national academies. This lack of recognition discourages participation by highly qualified people. The resulting vacuum brings out baser means of recognition—such as greed—in some.

3. *Product managers who don't understand the science often control the purse strings in the pharmaceutical industry.* Bright marketing people who have worked their way up to product manager are either openly hostile to or moderately intolerant of research and development (R&D), the depatment with which they battle for control over the company's future. Product managers may be impressed by slick dog-and-pony shows in direct proportion to the number of years of product exclusivity remaining. Another company's success with a totally unrelated product may be interpreted as proof of a delivery technology for the product in hand.

4. *R&D people don't want to be perceived as "nay-sayers."* With no internal solutions to the problem, R&D is tempted to shed its aversion to approaches "not invented here", laying the blame externally when they fail. After saying "no" to the product manager for six days, on the seventh they rest and say "yes"—often to systems that are scientifically shoddy.