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Advanced Drug Delivery Reviews 54 (2002) 457–458

Advanced
DRUG DELIVERY
Reviews

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Commentary

The origin of pegnology

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In the late 1960s when I was, as they say, between grants, I became interested in developing a procedure whereby selected bioactive proteins could be utilized for human therapy. This was at a time when human-derived proteins through recombinant DNA were not generally available, and although a few proteins of non-human origin such as insulin and asparaginase could be administered parenterally, most foreign proteins produced adverse immunological responses if injected into humans. Rutgers University, where I was a professor of biochemistry, has excellent libraries, and I spent the next few months in library work, educating myself in my new field and seeking an answer to the problem of how to provide the benefits of non-human bioactive proteins to humans. A word about the libraries of that time. They were marvelous places. Rows of chemical, biological, and medical abstracts with their multiple indexes going back many years, banks of card catalogues where the library's holdings were listed and crosslisted, shelves of all of the major and most of the minor periodicals of that era where one could read and browse for hours, and in an adjacent wing the bound volumes, where the references collected from the abstracts and current journals could be looked up. There was not a computer in sight; the only piece of electronic equipment was the photocopy machine, of which I made ample use.

What I found in my library studies, and a few meetings I attended, was that the number of investigators, using various approaches to solve this problem, was limited, and progress was steady but appeared to be slowed in many instances by adverse immunological responses. I eventually concluded that attaching a hydrophilic polymer, for example a fragment of dextran, glycogen, or some such biopolymer, might make the proteins less immunogenic. One day, however, while browsing in a medical journal, I came across an interesting article that related how physicians infused a solution containing a mild surfactant, a block copolymer of polyethylene glycol and polypropylene glycol, into the blood of patients undergoing major vessel surgery in order to prevent the formation of lipid embolisms. This was when I realized that polymers of this type had a medical use. Up to this point I had considered them to be industrial or commercial polymers. I read much of the literature (mainly commercial) on this class of copolymers, and at some point decided to focus on polyethylene glycol (PEG), the more hydrophilic of the pair. The more I read about it the more interested I became. PEG was soluble in several organic solvents, but was readily precipitated by adding certain other solvents, which would facilitate activation and recovery of the PEG, and it was soluble in aqueous solutions by virtue of bonding several molecules of water per ether oxygen. The ideal hydrophilic polymer. Flexible, unbranched, and with only terminal hydroxyl groups available for activation and linking to proteins. The toxicological literature revealed that PEG of higher molecular weights was nontoxic in various animals in the amounts that might be injected as a PEG-protein. It obviously was

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0169-409X/02/$ – see front matter
PII: S0169-409X(02)00021-2

worth further study. I requested a list of products from a major manufacturer of PEGs, meanwhile mulling over how, to prevent crosslinking, I might selectively activate only one of the two hydroxyl groups on bifunctional PEG (or how to fractionate the mix of unactivated, singly activated, and doubly activated PEGs that would undoubtedly be present in the activation mixture). When I opened the company's catalog, I found myself looking at the answer: monomethoxy PEGs of about 2000 and 5000 daltons, each with a single hydroxyl group awaiting activation and attachment to proteins. The final link in the chain, so to speak. I obtained samples of the monomethoxy PEGs and headed for the lab. Our coupling technology yielded PEG-proteins that showed not only greatly reduced immunogenicities upon IV injection in animals, but of equal interest, much longer circulating lives than their unpegylated counterparts, even on the initial injection when no antibodies were present. With the advent of human-derived proteins, enhanced circulating life seems to be the more important finding.

This is how pegnology started with my group. It was essentially a library operation. I can only hope that the modern science library with its banks of computer workstations and greatly reduced subscriptions to journals (''they're online'') can provide the same opportunities for searching, reading, and especially browsing, that the libraries of my time did.

Some final comments. The major advances in biology and medicine in the last 20–30 years appear to have been matched by the advances in pegnology. Certainly the research being done now is light-years beyond our simple studies of many years ago. I'm deeply impressed and indeed humbled by how pegnology has grown, and look forward to reading about the accomplishments of the next few years.