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Editorial

Advances in Targeted Drug Delivery

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It was just over a hundred years ago that the famous Paul Ehrlich put forward his theory of "the magic bullet", as an approach to overcome and tame different disease states. Among these, targeting to the cancer cells in varying bodily locations (organs) is of prime interest. Scientists have ever since worked on the principle of drug targeting, based on this idea of specifically delivering various drugs to diseased cells. Of particular interest are anticancer, biotherapeutic, genetically engineered and protein/peptide based drugs.

Progress in the field of drug targeting has been slow till thirty five years ago. With the advent of the monoclonal antibody technology in the mid seventies of the last century as well as the development of liposomal and polymeric nanoparticle carriers, the drug targeting field enjoyed a welcoming expansion and the clinical applications of these novel drug delivery systems became a feasible aim. Monoclonal antibodies, liposomes, polymers, proteins and many other entities have ever since seen the light as carrier molecules, and as with most technological developments, have all encountered a vast array of difficulties. They range from problems in the synthesis of the carriers and drug conjugates to unfavorable pharmacokinetics and toxicity. Furthermore, lack of knowledge on the anatomical and physiological barriers in the body have hampered their clinical application. However, many problems have been solved, not in the least due to the advent of recombinant DNA technology to construct better defined carriers that can be produced in large amounts, and advanced pharmaceutical formulation technology. Similarly, the rapid developments in molecular biology, cell biology and immunology led to a better understanding of the processes taking place in vivo upon administration of carriers and conjugates.

Only a few polymer or protein based drug targeting strategies have successfully reached the clinic and an important question in the coming years will be whether these strategies eventually will reach the international drug market. All will depend on their effectiveness and improved toxicity profiles as compared to free drug only and the ease of their production at large scale. Furthermore, it should be pointed out that the most promising drug carrier devices have been liposomes and biodegradable polymeric nanoparticles, being targeted to various bodily parts, mainly using the active drug targeting strategy via antibodies.

An important and novel area to be considered in drug targeting is conditional gene expression, which could be regarded as the control of protein delivery from within cells. The key to this strategy in the future will be to regulate gene expression engineered promoters. Regulatory systems could be designed, from individual regulatory elements, to promote expression in the presence of specific transcription factors which are over-expressed in tumors. This requires detailed knowledge of the control of gene expression in different tumor types. The design of specific promoters from scratch is not a realistic prospect at present. There is not enough knowledge on how different regulatory elements combine and how they need to be structured to achieve specificity. At present interest is focused on promoters of genes which are known to be over-expressed in tumors. The literature on this subject is expanding rapidly, and offers a better approach to cancer gene therapy than the use of viral promoters. When viral vectors are used for cancer gene therapy, the control of viral replication within tumors could offer a complementary level of specificity, provided targeted replication can be achieved safely. The

specificity of gene therapy can also be improved by ensuring that the delivery vector reaches its target cell surface. In the case of non-viral gene therapy this could be achieved using ligands expressed at the surface of the delivery particle. When viral vectors are used it is possible to engineer expression of an appropriate ligand on the surface of the viral particles, perhaps retargeting the virus from its natural target to a therapeutic target. In addition there are physical methods of retargeting using antibodies, fusion proteins or coupling polymers or ligand to the surface of the viral particle.

Since the early 1980' s there has been steady interest in the targeting of drugs or glycoprotein toxins to specific cells, a concept which was given strong impetus when monoclonal antibodies became widely available in the late 1970' s.

Another interesting issue to be considered is the concept of targeting hypoxic tissue. This strategy involves constructing linkers which are susceptible to breakdown under condition of hypoxia, which is common in cancer and several other indications. The strategy can be used to release a low molecular weight therapeutic agent selectively in hypoxic tissue, to reduce side effects of the agent.

Yet another important issue to consider is the use of cyclodextrin derivatives to modify distribution of oligonucleotides. Cyclodextrin derivatives appear to modify both uptake and stability of oligonucleotides, and their biocompatibility makes them a candidate to achieve 'passive' targeting and improved delivery.

Various strategies have been discussed in the literature for targeted delivery of therapeutic agents to hepatic, renal, pulmonary, brain, blood and bone cells for different clinical or diagnostic purposes. Nevertheless, as mentioned above, relatively few products have reached the commercial drug market, and this rather interesting and yet complex and fascinating drug delivery method seems to be in its infancy stage. However, currently, extensive studies are being conducted by numerous research groups worldwide and we expect to see a broad range of these drugs becoming available to general public for treatment of different ailments in the coming years. In fact targeted drug delivery systems could be looked upon as the new generation of drug delivery systems, which could overtake the drug market in the near future.

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