ACCOUNTS
of chemical research

GUEST EDITORIAL

Introduction to Gene Silencing and Delivery

The pills we take release small drug molecules that can permeate the numerous membranes and other physiological barriers between the digestive tract and the drug's site of action. This is a consequence of the balance between drug affinity, cell permeability, and water solubility achieved by contemporary medicinal chemistry. A few diseases offer unique targets not present in normal cells; this permits targeted therapies, such as the drug Gleevec binding specifically to the mutant bcr-abl protein. However, in many cases, the target is a normal protein whose activity we wish to adjust in some cells but not others. While we might prefer to develop a smarter small drug molecule with added special properties for finding only certain cells, the way forward is filled with formidable fundamental challenges. The same might be said about this issue's topic. The need for more elaborate features gives rise to larger, more complex molecules and the science of drug delivery.

In contrast to small drug molecules that affect the *function* of a target protein, the specific base-pairing properties of nucleic acids seem to offer a natural foundation for exquisitely altering the *synthesis* of key proteins in selected cells by adjusting the local level of gene expression. This includes the introduction of a gene for a functional protein to correct a genetic defect, which was the original concept of gene therapy. In addition, the ability to control individual gene expression has important applications to basic studies of cell biology *in vitro*. The power to strongly reduce or even eliminate the expression of an individual gene in a cell, without making mutants, gives the researcher an opportunity to study how the cell works in unprecedented detail. Controlling the timing of gene expression offers opportunities that are even more interesting.

Turning this biology into chemistry is a stimulating challenge to the imagination and ingenuity of the experimentalist. The laboratory tools to accomplish this have never been better. We can synthesize polymers with a defined sequence of residues, and those residues can be nucleotides, amino acids, carbohydrates, any of a huge collection of organic units such as ethylene glycol, or combinations of these. We can link polymers together precisely using orthogonal conjugation techniques, and we can characterize the products with a remarkable array of advanced analytical methods.

However, a delivery problem must be solved: nucleic acids are not small molecules, and they carry a polyionic negative electric charge. This state of affairs is different from small drug molecules and demands a different technical approach. The biology of viruses provides useful models for purely synthetic approaches to specific gene control. Viruses can do it all: remain stable in hostile environments, suspend readily in biological media, recognize potential host cells, introduce viral nucleic acids into those cells, and divert the cells' gene expression processes to the virus' advantage. The current state of HIV therapy illustrates the complexity of one important class of viruses and the highly sophisticated tools scientists have developed to control it.

Can we adapt a natural virus to the task of delivering therapeutic nucleic acids? Many researchers are exploring that, though there are some concerns about unintended consequences. The Accounts in this issue address this question on a case-by-case basis, frequently choosing nonviral approaches to nucleic acid delivery. The mechanistic challenges to be overcome always involve molecular transit from the outside medium to the cell surface, through the membrane and inner compartments, to the intracellular location of the target RNA or DNA. In some instances, the experimental plan also includes selective uptake of synthetic particles in a small number of target cells while in the presence of a large number of very similar nontarget cells.

Twenty-one Accounts in this issue describe aspects of targeting nucleic acids into living cells *in vitro* and *in vivo*. Some of these are wonderful memoirs recounting progress from the earliest days of gene therapy and summarizing a wealth of experimental results. Others deal primarily with

Published on the Web 07/17/2012 www.pubs.acs.org/accounts
10.1021/ar300157k

the chemical and biological aspects of synthetic carriers of increasing complexity, from the laboratory bench to clinical trials. We hope that the overall result for the reader will be an informed picture of the state of this art, where it has been, and where it is likely to go.

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