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Dr. Felgner has been involved in academic research and the biotechnology industry since 1972 with graduate (Michigan State University) and post-graduate (University of Virginia) training in biochemistry and biophysics. Most recently his work has emphasized aspects of drug delivery and gene therapy research. Prior to founding the Vical gene therapy business in 1990, he was Staff Scientist at Syntex Research, where he invented the first cationic lipid (Lipofectin™ and LipofectAMINE™, Gibco, BRL) reagents for gene transfer¹. For his numerous biotechnology innovations (12 issued domestic patent applications) Dr. Felgner received the Southern California 1996 Inventor of the Year award. He has recently launched a new business called Gene Therapy Systems, Inc., with the mission to provide more innovative tools to academic scientists and pharmaceutical companies interested in gene therapy research and pharmaceutical development.

1. Felgner, P.L. et al. *Proc Natl Acad Sci USA* **84**, 7413-7417 (1987).

PNA-Dependent Gene Chemistry to Control Plasmid Delivery and Expression

Peptide nucleic acid (PNA)-dependent gene chemistry technology offers a novel, straightforward, and versatile approach to permanently introduce new physical and biological properties into plasmid DNA¹. This technology provides investigators with a powerful new tool to study signal transduction, to develop more efficient gene delivery systems and to produce more effective DNA vaccines.

PNA is an oligonucleotide analog that hybridizes in a sequence-dependent manner to its complementary DNA target. While most oligonucleotide analogs can bind with high affinity only to single-stranded nucleic acid targets, PNA can bind very tightly to double-stranded DNA^{2,3}. This binding property is the basis for the following reactions, which describe the fundamental scheme of PNA-dependent gene chemistry technology¹.

- 1) Plasmid + PNA* Plasmid-PNA*
- 2) Plasmid-PNA* + Ligand Plasmid-PNA-Ligand

Since PNA technology can be applied without destroying the transcriptional activity of the gene, it is particularly adaptable to medicinal chemistry, a classical approach for developing drug candidates. In medicinal chemistry, small molecules with biological activity are systematically modified, and tested for biological activity. Through this process, the attributes of small molecules are optimized for drug development. To date, a medicinal chemistry approach has not been possible with DNA because the methods used to modify DNA either reduce or destroy its ability to be transcribed. Since PNA/DNA hybridization is sequence-dependent, a plasmid can be constructed that contains a complimentary PNA binding site in a region of the plasmid that does not interfere with the promoter/enhancer or the coding region. Thus chemistry can be carried out on the PNA/DNA hybrid without destroying the activity of the gene.

Through PNA technology, plasmids can not only be modified, they can be customized for particular experimental systems. For applications in gene therapy, proteins and peptides can be attached to plasmid DNA to improve its delivery and expression. Fluorescent- or biotin-labeled plasmids are ideal for monitoring gene delivery. Numerous applications for PNA chemistry are possible in the development of DNA vaccines, where the addition of immunostimulatory oligonucleotides could enhance the immune response to expressed antigens. Alternatively, the activity of specific viral proteins could be studied by binding the proteins to plasmids and examining their influence on gene delivery and expression. Similarly, the attachment of transcription factors or transcription factor analogs to plasmids could be used to test for activity in signal transduction pathways. An update summarizing the applications of this technology will be provided.

1. Zelphati, O. et al. *Human Gene Ther.* **10**, 15-24 (1999).
2. Egholm, M. et al. *Nucl. Acids Res.* **23**, 217-222 (1995).
3. Demidov, V.V. et al. *Proc. Natl. Acad. Sci. USA* **92**, 2637-2641 (1995).