Background, potential disease targets for gene therapy

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Contact: Yvonne Baskin, (619) 534-3120

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BACKGROUND: POTENTIAL DISEASE TARGETS FOR GENE THERAPY

Five years ago, the dream of treating human disease by transplanting genes focused on rare congenital disorders such as Lesch-Nyhan Syndrome, thalassemia and inherited immune deficiencies.

Now, even before gene therapy has reached the bedside, the potential targets have expanded to include such common afflictions as cancer, heart disease and brain disorders.

Theodore Friedmann, M.D., a University of California, San Diego pediatrician and molecular biologist, has been working on developing gene therapy models for the past 20 years, with special emphasis on brain disorders such as Lesch-Nyhan, a cerebral palsy-like disease.

"Lesch-Nyhan has been for us a model system to demonstrate ways of inserting new genes into various body tissues to supply missing functions," says Friedmann.

The approach involves using disarmed viruses as vectors or carriers to insert functional genes into bone marrow and, more recently, fibroblasts, liver and brain cells that can then be returned to the body.

"What we're seeing now is an exciting convergence between this basic genetic research and a completely new kind of approach to clinical problems," Friedmann says.

In September, Friedmann and a team led by Daniel Steinberg, M.D., director of UCSD's Specialized Center of Research on Arteriosclerosis, reported inserting foreign genes into rabbit cells to correct a defect of cholesterol metabolism. The work, published in the Proceedings of the National Academy of Sciences, involved the gene for low density lipoprotein (LDL) receptors and suggested a possible strategy for gene therapy in inherited heart disease.

Reports in this week's Science by Friedmann and two other UCSD teams led by Fred H. Gage and Wen-Hwa Lee demonstrate potential genetic approaches to brain disorders and certain cancers.

"No one is shy about using the words 'gene therapy' anymore," Friedmann noted. "It is a certainty now that diseases will be treated at the level of the genes. Many of the conceptual and public policy hurdles have now been cleared. The remaining questions are largely technical--what gene, what vector, what tissue?"

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