Synopsis

A forward leap in new therapies

Gene-based technology which may result in the development of new drugs is gaining ground and recent successes have paved the way for previously unthought-of therapy.

Golden eggs

The Merriam Webster Collegiate Dictionary defines 'transgenic' as 'having chromosomes into which one or more heterologous genes have been incorporated either artificially or naturally'. Many companies are turning to transgenic chickens as a 'pharmaceutical bioreactor' which can meet the demand for protein-based therapeutics. A foreign gene is inserted to stimulate them to produce human proteins in egg whites. A new wave of health products is expected which may be 'golden eggs' for the pharmaceutical companies. Already over 300 human antibodies have been concocted in laboratories and have been tested against ailments such as cancer, viral diseases and immune deficiencies.

The making of drugs in chicken eggs is mathematically and economically appealing: the final cost of purified protein should be about 100-fold less than currently used cultured mammalian cells. Chicken flocks are easy to ramp up and chicken farms are already secure enough to prevent the birds from escaping into the wild and breeding.

But despite all the optimism and reports of triumph, true success has eluded scientists. Joe Alper, writing in *Science*,[1] says that scientists were despondent about the failure to get the genes to carry over to succeeding generations of chickens or else chickens failed to produce the desired proteins in the eggs. Ann Gibbins, of the University of Guelph in Ontario, Canada, said, 'It left us all thinking that it was going to take some kind of magic to ever make a transgenic chicken egg.' Alper replies, 'The magicians have arrived.' Proof-of principle experiments have been successful for at least three research teams, and while nobody has a transgenic chicken ready to produce a pharmaceutical today, it is imminent according to scientists involved in the research.

Researchers at BioAgri in California are taking a different tack. They are working with rooster sperm. They have a monoclonal antibody which binds to the surface of the sperm and allows DNA linked to the antibody to enter the sperm cell and incorporate itself into the sperm's genome. Using this technique, biologists have created two different transgenic chickens which produce human interferon alpha and interferon beta.

Gene silencing

According to David Stipp, writing in *Fortune* magazine,[2] 'advances that win Nobel prizes are uncommon, ones worth billions of dollars are even scarcer, and those yielding both are blue-moon rare ... Now there's a spellbinding blue glow on biotech's horizon again.' He is talking about RNA interference (RNAi). RNAi is an endogenous gene-specific silencing technique, knowledge of which was first obtained from plants and expanded in the nematode Caenorhabditis elegans. It probably exists to fend off pathogens and to control gene expression. It has now been harnessed to silence genes causing human disease potentially treating such conditions as Huntington's disease, cancer and some viral diseases where it would be desirable to 'switch off' certain genes that cause problems.

Genetically based disease can result from inheriting a mutated gene copy, but it could also come from random mutation of one or both copies (depending on whether it is dominant or recessive, respectively). Researchers at the University of Iowa (UI) have shown that it is possible to silence a mutant gene without affecting the expression of the normal gene. They have learned that a single nucleotide difference between a normal gene and a mutant gene can be used to turn off the mutant gene. 'It is an intellectually simple but technologically difficult thing to do,' says Victor Miller, one of the UI researchers. RNAi would be particularly useful in the dominantly inherited diseases like Huntington's. They have successfully silenced a mutant gene causing the neurodegenerative condition known as Machado-Joseph disease (MJD or spinocerebellar ataxia type 3) while leaving the normal gene alone. The genetic defects in other neurodegenerative diseases such as Alzheimer's and Parkinson's disease produce a clumping together of a mutant protein, which appears to damage brain tissue. Initial attempts to silence the MJD gene by targeting the RNA itself failed, so the UI researchers focused on a single sequence difference also known as a single nucleotide polymorphism (SNP) which occurs just next to the mutated sequence in about 70% of mutant MJD genes. They achieved success when they targeted that single nucleotide variation which only silenced the mutant gene, leaving the normal gene intact.

Henry Paulson, Assistant Professor of Neurology, says 'NA interference is an exciting new tool that may have therapeutic value. If we can use this to target a disease gene exclusively, it will be very valuable.'

Will the development of new therapies based on these techniques signal the disappearance of certain diseases just as smallpox has disappeared? Time will reply, but with these novel technologies, it seems that there is reason for optimism.

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1. Alper J. Hatching the golden egg: a new way to make drugs. *Science* 2003; **300**: 729 -730.
2. Stipp D. *Fortune*, May 12, 2003. *Fortune* Online: **http://www.fortune.com/fortune/technology/articles/0,15114,450721**