BOOKS: MEDICINE

Gene Therapy Enters Adolescence

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More than 100 years ago Louis Pasteur observed "there does not exist a category of science to which one can give the name applied science. There are science and the applications of science, bound together as the fruit to the tree which bears it." Never has this metaphor been more true than in the emerging field of human gene therapy, which has promised to revolutionize the practice of medicine over the next 20 years. The conceptual seductiveness of gene therapy derives largely from its powerful simplicity. Rather than attempting to treat diseases with small molecules that transiently ameliorate the metabolic disorders resulting from genetic defects, gene therapy proposes to correct the genetic defects themselves. Despite the promise of this concept, the field has bitterly disappointed both its most ardent proponents and the scientific community at large for more than two decades. The reality of translating gene therapy into clinical practice has been severely impeded by basic biological and technological problems that have only recently begun to yield to novel experimental approaches.

The Development of Human Gene Therapy
Theodore Friedmann, Ed.
Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1999. 743 pp. $134. ISBN 0-87969-528-5.

The relatively brief history of this field provides fascinating insights into the complex interplay of basic science, technology, business, and medical ethics that shapes much of modern biology and medicine. The foundations of gene therapy are firmly rooted in the rapid advances in molecular genetics, cell biology, and virology of the 1950s and 1960s. As early as 1964, several investigators including Lederberg, Kornberg, and Tatum suggested that it might be possible to introduce genes into mammalian cells in order to obtain therapeutic effects. The first human gene-therapy experiment appears to have been carried out in the early 1970s, when Stanfield Rogers administered Shope rabbit papillomavirus to two girls suffering from arginemia. Although based on the interesting observation that animals infected with this virus displayed reduced levels of serum arginine, this trial failed to demonstrate any evidence of clinical efficacy.

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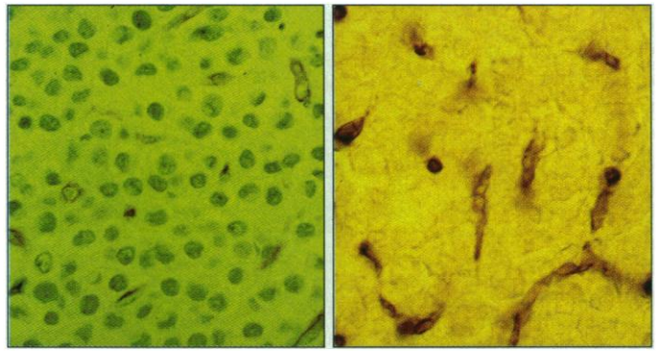
There was little further progress in gene therapy until the mid 1980s when advances in viral vectors, gene cloning, and in vitro transfection techniques led to a veritable explosion in both pre-clinical and clinical gene-therapy experimentation. The tremendous enthusiasm of early investigators in the field was rapidly communicated to the lay press, who touted gene therapy as the answer to many previously untreatable human diseases from cancer to heart disease and AIDS. This exuberant optimism only increased the frustration and disappointment as one major human gene-therapy trial after another failed to demonstrate any clinical efficacy. Almost lost in these disappointing results was the fact that the overwhelming majority of these early phase I gene-therapy trials were not designed to demonstrate efficacy at all, but instead were designed to assess the safety of transferring cloned genes into humans. And without question, these approaches were safe; remarkably little morbidity and no mortality have been seen in the hundreds of patients treated to date.



Tumor cell cuffs. In breast cancer, capillary vessels are surrounded by a microcylinder of three or four layers of tumor cells. (Left, 4-μm-thick histologic section stained to highlight blood vessels; right, 50-μm-thick confocal microscopy section.)

The failures of the initial experiments provided investigators with sobering and important insights into the biological problems that needed to be overcome before gene therapy could become clinically useful. In particular, three problems seemed responsible for the observed lack of efficacy: (i) difficulties in efficiently transducing primary quiescent (G0) human cells in vivo, (ii) powerful immune responses (to both the gene-therapy vectors and the foreign therapeutic transgenes) that rapidly eliminated transgene-expressing cells in humans, and (iii) the ability of many cell types to shut off the viral promoters that were being used to control transgene expression in humans. By 1993, these observations led most researchers in the field to suspend human experimentation. In an attempt to better understand and circumvent these problems, investigators returned to basic studies of virology, immunology, and gene expression.

During the last five years these basic scientific efforts have paid off handsomely. The engineering of new vectors including adenoviruses, adeno-associated viruses (AAV), and lentiviruses promises to greatly enhance the efficiency of in vivo gene delivery and to simultaneously reduce the immunogenicity of both vectors and transgenes, thereby leading to stable and high-level transgene expression in immunocompetent animals. The characterization of cellular and regulatable promoter systems promises to provide new tools with which we can regulate transgene expression in humans in both a tissue-specific and physiologically or pharmacologically responsive fashion. Finally, the cloning and sequencing of large numbers of new human genes and a better understanding of the genetic bases of human diseases have significantly expanded the scope of diseases that may be amenable to gene-therapy approaches. Given these recent advances, publication of *The Development of Human Gene Therapy* could not be more timely. The book, a compendium of review articles by leaders in the field edited by Theodore Friedmann (one of the founders of modern gene therapy), is divided into two sections. The first provides an up-to-date, comprehensive overview of the major vectors used in current gene-therapy experiments, from adenoviruses to lentiviruses and naked DNA. The second discusses some human diseases that might respond to gene therapy, including select hematologic, neurologic, and infectious diseases.

The volume will be especially useful to students interested in educating themselves about the current state of the art of

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gene therapy and to investigators in the field who are looking for a quick update on topics outside of their areas of expertise. Its particular strengths include a comprehensive, up-to-date summary of existing vectors, the superb chapter on emerging viral vectors by D. Jolly, the chapter on angiogenesis by J. Folkman and co-workers, and the chapter on apoptosis by J. Reed. Given the recent improvements in gene-delivery technology, we will soon be facing important new ethical issues about both germ-line gene therapy and enhancement therapies designed to effect heritable traits such as height, weight, strength, and even intelligence. E. Juengst and L. Walters lucidly discuss these approaching dilemmas in their chapter on the ethics of gene transfer research.

In spite of these strengths, readers may come away from the book disappointed. Like almost all multi-author compendia, the volume suffers both from a lack of cohesiveness and from significant redundancies among related chapters. Students, in particular, could have benefited from the inclusion of summary chapters that compared the different approaches to gene therapy, the different vector systems currently in use, and the types of diseases that might be targeted with this technology. More important, although the book is more than 700 pages long, it, somewhat surprisingly, lacks coverage of many important topics. For example, none of the chapters considers gene-therapy approaches to cardiovascular disease, autoimmune disorders, serum protein deficiencies, or dermatological diseases. Similarly missing are descriptions of germ-line gene modification and alternative ways to alter gene expression (including the use of antisense oligonucleotides, ribozymes, artificial chromosomes, or homologous recombination). There is no discussion of new approaches for regulating transgene expression in vivo or recent advances in gene delivery devices. Many of these topics represent the future directions of the field, and their inclusion would have both strengthened the book and increased the longevity of its usefulness.

Despite these deficiencies, *The Development of Human Gene Therapy* is a timely and useful book that highlights the significant recent advances in the field. At the same time, it illuminates the important hurdles that remain to be overcome en route to a clinically useful reality. As Pasteur would have predicted, our ability to move gene therapy forward into the clinic will depend entirely on continued basic scientific advances. The recent rapid pace of these advances augurs well for the future of the field.

CD-ROM: ASTRONOMY

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As you hover over the outermost Galilean satellite Callisto, you see the bold orange and cream-colored clouds of Jupiter slowly brighten while the sun rises over the planet's limb. Although this may sound like the latest science-fiction movie, it is actually a view you can easily set up on your home computer with Starry Night software.

Starry Night Pro
by Sienna Software Inc.
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$149, C$199.
416-410-0259
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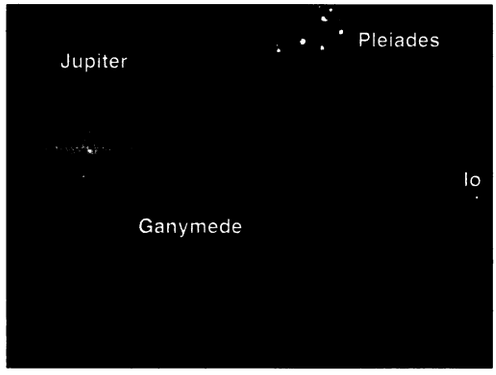
Albrecht Dürer's woodcuts of the constellations (1515) were the first printed star charts. Like more modern star charts, they depict the positions of objects in the night sky visible from Earth. Early computer-driven star charts were also Earth-centered, although producing maps of the heavens, even fairly simple ones, on the computer offers significant advantages over paper versions. Users can view the sky from any location on Earth at any specified time; they can also follow the picture forward (or backward) through time. Some more recent astronomy software packages provide views from extraterrestrial locations, but the possibilities are limited and the graphics remain simple. Starry Night, which can be run on both Windows and Macintosh platforms, represents a substantial improvement in this class of software.



Orbiting Jupiter. Starry Night's depiction of the Galilean moon Ganymede viewed from 2000 km above the north pole of Callisto at 22:00 UT, 30 September 1999.

Upon starting the program, the user is presented with a view of the current sky over their home location. Various easy-to-use graphical menus allow manipulation of the time, location, direction, and field of view. Starry Night Pro lets the user choose locations on (or above) nearly any solar system object or anywhere within 20,000 light years of Earth. One can scan the skies from Pluto; enjoy the view from Halley's Comet as it approached Earth in 1910; or position oneself a few hundred million kilometers over the sun's northern pole, compress time, and watch the planets speed along their orbits.

Other astronomical software packages provide many of the same functions, but Starry Night has additional features that set it apart. As more detailed maps of the surfaces of solar system objects become available, these images can be loaded into the software's files. Additional objects, such as the two irregular moons of Uranus reported last year, can be entered into the virtual solar system, allowing accurate charting of the motions of newly discovered comets, asteroids, or moons. The Pro version allows users to add custom data files and to substitute photographs or charge-coupled device images for the default pictures. Starry Night is somewhat limited in the information it provides on celestial objects. The 110 Messier objects (nebulae, galaxies, and star clusters), for example, are displayed with only limited descriptive data. Although the LiveSky feature indexes more detailed information and images, an Internet connection must be maintained for its use. Other packages might be better suited for amateurs desiring an Internet-independent, comprehensive deep sky database complete with high-quality graphical images.

As an educational tool, Starry Night is excellent. The integrated Hipparcos stellar data can be used to generate dynamic Hertzsprung-Russell diagrams (plots of absolute magnitudes against spectral types) for star clusters or groups. With the movie function, views of any celestial event can be recorded and saved in the standard QuickTime format; the resulting electronic movies can be played back with the common Internet browsers.

Sienna supports Starry Night through an extensive electronic help manual and a detailed web site. Users can also download updates and additional information on celestial objects. For a reasonable price, the Starry Night package provides all the basic functions of an electronic star chart along with the utility of a small planetarium, detailed images of celestial objects, and limited physical data on the many wonders of the night sky.

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