as well as goal-oriented research contributing to human welfare. While, governments in general should be helped to decide on priorities, gene therapy as such has tremendous possible applications for mankind and sweeping generalities will only harm a great cause. Let us not straight jacket issues and make scientists appear as in 'white coats for self-preservation'. The community is as much interested in human welfare as any one else professing the same.

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NEWS

Report and recommendations of the panel to assess the NIH investment in research on gene therapy

Executive summary of findings and recommendations

Dr Harold Varmus, Director, National Institutes of Health (NIH), appointed an *ad hoc* committee* to assess the current status and promise of gene therapy and provide recommendations regarding future NIH-sponsored research in this area. The Panel was asked specifically to comment on how funds and efforts should be distributed among various research areas and what funding mechanisms would be most effective in meeting research goals.

The Panel finds that:

1. Somatic gene therapy is a logical and natural progression in the application of fundamental biomedical science to medicine and offers extraordinary potential, in the long-term, for the management and correction of human disease, including inherited and acquired disorders, cancer, and AIDS. The concept that gene transfer might be used to treat disease is founded on the remarkable advances of the past two decades in recombinant DNA technology. The types of diseases under consideration for gene therapy are diverse; hence, many different treatment strategies are being investigated, each with its own set of scientific and clinical challenges.
2. While the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol, despite anecdotal claims of successful therapy and the initiation of more than 100 Recombinant DNA Advisory Committee (RAC)-approved protocols.
3. Significant problems remain in all basic aspects of gene therapy. Major difficulties at the basic level include shortcomings in all current gene transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host.
4. In the enthusiasm to proceed to clinical trials, basic studies of disease pathophysiology, which are likely to be critical to the eventual success of gene therapy, have not been given adequate attention. Such studies can lead to better definition of the important target cell(s) and to more effective design of the therapeutic approach. They often can be carried out in appropriate animal models. Pathophysiologic studies may also suggest alternative treatment strategies.
5. There is a clear and legitimate need for clinical studies to evaluate various aspects of gene therapy approaches. Although animal investigations are often valuable, it is not always possible to extrapolate directly from animal experiments to human studies. Indeed, in some cases, such as cystic fibrosis, cancer, and AIDS, animal models do not satisfactorily mimic the major manifestations of the corresponding human disease. Clinical studies represent not only practical implementation of basic discoveries, but also critical experiments which refine and define new questions to be addressed by non-clinical investigation.
6. Interpretation of the results of many gene therapy protocols has been hindered by a very low frequency of gene transfer, reliance on qualitative rather than quantitative assessments of gene transfer and expression, lack of suitable controls, and lack of rigorously defined biochemical or disease endpoints. The impression of the Panel is that only a minority of clinical studies, illustrated by some gene marking experiments, have been designed to yield useful basic information.
7. Overselling of the results of laboratory and clinical studies by investigators and their sponsors – be they academic, federal, or industrial – has led to the mistaken and widespread perception that gene therapy is further developed and more successful than it actually is. Such inaccurate portrayals threaten confidence in the integrity of the field and may ultimately hinder progress toward successful application of gene therapy to human disease.

Based on these findings, the Panel recommends the following:

1. In order to confront the major outstanding obstacles to successful somatic gene therapy, greater focus on basic aspects of gene transfer, and gene expression within the context of gene transfer approaches, is required. Such efforts need to be applied to improving vectors for gene delivery, enhancing and maintaining high level expression of genes transferred to somatic cells, achieving tissue-specific and regulated expression of transferred genes, and directing gene transfer to

*Stuart H. Orkin and Arno G. Motulsky, Co-chairs.

specific cell types. To stimulate innovative research, the Panel recommends the use of interdisciplinary workshops, specific programme announcements in these areas, and the use of short-term, pilot grants for testing new ideas and for encouraging investigators from other areas to enter the field of gene therapy.

2. To address important biological questions and provide a basis for the discovery of alternative treatment modalities, the Panel recommends increased emphasis on research dealing with the mechanisms of disease pathogenesis, further development of animal models of disease, enhanced use of preclinical gene therapy approaches in these models, and greater study of stem cell biology in diverse organ systems.
3. Strict adherence to high standards for excellence in clinical protocols must be demanded of investigators. Gene therapy protocols need to meet the same high standards required for all forms of translational (or clinical) research, whatever the enthusiasm for this (or any other) treatment approach.
4. To enhance the overall level of research in this area, the Panel recommends that NIH support broad interdisciplinary postdoctoral training of M D and Ph D investigators at the interface of clinical and basic science. Mechanisms for physician training in this area might include use of career development awards based on a programme announcement in gene therapy.
5. Investigators in the field and their supporters need to be more restrained in their public discussion of findings, publications, and immediate prospects for the successful implementation of gene therapy approaches. The Panel recommends a concerted effort on the part of scientists, clinicians, science writers, research advocates, research institutions, industry, and the press to inform the public about not only the extraordinary promise of gene therapy, but also its current limitations.
6. NIH has already provided an appropriate initial investment in gene therapy. Future gene therapy research should compete with other forms of biomedical research for funding under stringent peer review. Only with fair, yet critical, peer review will high standards be met and maintained. The Panel specifically does not recommend special gene therapy study sections, expansion of existing centre programmes in gene therapy, or expansion of the recently funded core vector production programme. To ensure that the level of support remains appropriate, the NIH investment in this field should be reexamined periodically.
7. To enhance the contribution of industry to the field, the Panel recommends that NIH encourage collaborative arrangements between academic institutions and industry that complement NIH-supported research, and also implement mechanisms that facilitate the distribution and testing of vectors and adjunct materials for use in clinical studies.
8. In an effort to improve gene therapy research and reduce duplication of effort, the Panel urges better coordination and scientific review of such research throughout the NIH Intramural Programme. In addition, NIH Institute Directors should resist pressures to include gene therapy research in their portfolios (either intramural or extramural) to 'round out' their programmes or compete with other Institutes. Instead, they should include such research only when there are compelling scientific reasons to go forward. Institute Directors should take the lead, where it seems appropriate, to focus efforts on improvement of diagnosis and understanding of disease pathogenesis and await further developments in vector technology before expanding clinical gene therapy programmes.

Asteroids and Earth's evolution – A new perception

Shaking the very foundations of long-accepted geological and geophysical theories, some new unorthodox views which cannot be brushed aside have been put forward by H. R. Shaw, a researcher in the US Geological Survey, in his recent book *Craters, Cosmos and Chronicles: A New Theory of Earth* (Stanford University Press). Shaw feels that asteroids and comets had a much greater role in shaping Earth's geological evolution than has been presumed so far. These celestial bodies did not impact randomly all over Earth, but hit only particular spots, determined by their nonlinear interactions with members of the solar system. The repeated batterings that the Earth has taken in its long past have contributed to the various geophysical phenomena like the distribution of continents, disposition of Earth's magnetic field, triggering of volcanic eruptions and the evolution and extinction of life forms.

Along with colleague William Glen, he chronicled several asteroid impacts between the time period 50–100 million years ago, and surprisingly found that their impact sites fell along a line encircling the globe, which they aptly called the K–T swath, after the famous asteroid impact during the Cretaceous–Tertiary period (Figure 1). Still older impact sites dating back to 600 million years ago were also found to group into three distinct clusters in North America, Eurasia and Australia, instead of being randomly distributed among all continents.

Shaw feels that chaos arising from nonlinear interplanetary gravitational influences dictates the orbits assumed by asteroids which are believed to have been ejected out of the main asteroid belt. Their chaotic trajectories bring them into inner solar system, where they come within the grip of the Earth (or other inner planets) and once within its influence, the uneven distribution of mass inside the Earth causes the paths of these asteroids to shift gradually to specific orbits, in tune with the fluctuating gravity profile over the Earth. In due course, they end up crashing to the Earth, always along circular tracks corresponding to their gravity-tuned trajectories. According to Shaw, these bodies have been crashing along a limited array of sites or 'cratering nodes' over the past half-billion years.