

# A Prescription for Gene Therapy

## The First Cabo Gene Therapy Working Group<sup>1</sup>

### FROM DIAGNOSIS TO PRESCRIPTION

Despite a growing number of diagnosticians solemnly listing the ills besetting gene therapy, too few prescriptions have been written. To mark the anniversary of 10 years of clinical gene therapy trials, a symposium entitled *Gene Therapy: Science, Application, and Ethics. Past and Future* convened this past March in Cabo San Lucas, Mexico. The purpose of this gathering of scientists, physicians, industry leaders, and bioethicists was to evaluate the accomplishments of the past decade, as well as the obstacles still preventing gene therapy from realizing its full potential.

The most oft-heard question raised by both the public and researchers is "why, after all this time, are there still no successful gene therapies?" Doug Jolly (Chiron) pointed out in his opening remarks to the assembled experts that this is, in fact, the wrong question to ask. The average time it takes to get any drug from initial work through to final approved product is 10 years, with an investment of more than \$100 million along the way. Considering that the very first gene therapy trial began only 10 years ago, with a fairly small base of knowledge, the real question should be how we have managed to come so far despite the substantial obstacles still facing gene therapy.

Although the subsequent meeting discussions ranged widely from razor-sharp debate to what could charitably be called "unfocused," these interactions yielded a consensus on some long-term strategies to be undertaken by scientists, the ASGT, industry, regulatory authorities, and educational supporters. Despite the distractions of the location, the meeting participants reached consensus on many substantial issues. More importantly, they outlined a series of concrete measures that may be undertaken to ensure the continued healthy growth of the field. The following details the agreed-on successes and obstacles and then outlines the specific proposals for moving ahead.

### THINGS AREN'T AS BAD AS THE POPULAR PRESS SAYS

First and foremost, we have learned that the simple central concept driving gene therapy is true: It is possible to put a gene into a patient and have that gene expressed safely. This may seem obvious now, but it was not so only a decade ago. Although certain gene products may be toxic at the wrong amounts and in the wrong place (which underlines the need for further studies on regula-

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tion of expression and vector targeting), the fact is that it *can* be done. Almost all the toxic effects seen to date have been related to the delivery system, in particular, the vectors used, not to the actual gene products.

The past decade has seen the development of a variety of different viral and nonviral vectors. It has also revealed the importance of matching the vector type with the target cell type or tissue and, thus, specific clinical indication. It is now known that no single vector will be applicable to all indications and that some vectors are likely contraindicated for some applications. Nevertheless, this is substantial progress. Improvements on the current vectors, in addition to the promising developments in nonviral delivery systems, need to continue, but the basic outlines are there.

A third important discovery of the past 10 years has been that preclinical animal models have generally predicted what is seen in clinical practice, at least in terms of toxicology. Although less successful in determining dosage, it is clear that current animal models are important and need to be built upon for future progress. Other animal models also need to be evaluated for their relevance in the use of particular vectors and disease. However, animal studies have been invaluable in the success of gene therapy to this point.

Although gene therapy is in its infancy and no consistent human clinical success is yet known, we can be encouraged by what one meeting participant dubbed the "phenomenology of success" seen in various trials over the past few years. *There is little doubt that some trial participants show positive clinical responses to gene therapy.* However, the mechanism and reproducibility of those responses need to be elucidated. Nevertheless, we should be encouraged by the possibility that things are "working," even as we struggle with our ignorance as to "how."

Finally, one very positive aspect of gene therapy's growth over the past decade has been the unparalleled cooperation between researchers and the regulatory authorities, most notably the U.S. Food and Drug Administration (FDA). Although we know that regulatory oversight and enforcement will become noticeably tighter in the near future, much of the progress made would have been impossible without a pragmatic and science-based approach from the FDA that assisted rather than impeded the remarkable growth of the field.

These positive signs of the health of gene therapy should continue to encourage basic scientists as well as clinicians pushing the boundaries of this nascent discipline. Nevertheless, progress has a way of illuminating problems as well as promises, and the Cabo gathering cast an unflinching eye on these as well.

#### ADVANCES HAVE BEEN MADE, BUT THERE ARE STILL BIG PROBLEMS

In many ways, the recent negative press suffered by gene therapy can be traced to the labyrinthine mountain of regulations that govern conductance of clinical trials.

This is not to impute guilt: rather, it underlines the fact that significant resources need to go into a trial, particularly in building the infrastructure necessary to dot every "i" and cross every "t." A host of reasons can be given for why this may not be achieved across current trials. The principle reason may be the lamentable lack of experience and training. Academic researchers, accustomed to the costs associated with equipment and lab workers, are less aware of the huge costs involved in regulatory issues and thus tend to underestimate personnel and systems needed to run such trials. This is the fault of neither the researchers nor the funding agencies alone. Current NIH funding provides for scientific pursuits but not the required regulatory infrastructure: This lacuna needs to be addressed not only by the funding agencies but also by the academic institutions themselves. The continuation of current trials or the approval of further trials without ensuring that the required clinical/data management/regulatory infrastructure is in place risks the possible endangerment of trial participants, whose safety must always be the foremost consideration, and merely begs for further public relations disasters.

The lack of sufficient regulatory attention is more than matched by a lack of public education that has magnified recent adverse events. Deaths or injuries from a gene therapy protocol have been viewed by the public through the media-made prism of conflict-of-interest, deviation from procedures, and a real fear of genetic "tinkering." An anecdotal decrease in the number of potential trial participants is only one symptom of the seriousness of this problem. It is clear that what few public education attempts have been made are inadequate to stem the growing tide of public distrust. There is a strong need to promulgate balanced information.

An even more intractable problem is the very real lack of standards and assays in the young field. At the December RAC meeting to consider the toxicity of adenoviral vectors, participants bemoaned the fact that it is almost impossible to compare dosages from trial to trial, as different researchers measure titers in different ways. This is true not only for adenovectors, but also for any of the vectors in current use. Compounding this initial problem in any trial is the fact that there are few assays available to track the delivery and/or expression of a transferred gene and often the relationship of the gene to the underlying disease process may be poorly understood. There are few good clinical surrogate markers for most diseases being tested with gene therapy. To date, resources and coordinating efforts for development of these critical tools are lacking and acutely needed.

Directions toward constructing such tools could be gleaned from the vast amount of data generated in the trials already completed or underway. The difficulty here is access: there is no central place one can go for a well-analyzed summary of these data, much less the mountain of raw material. For example, a rigorous "horizontal analysis" of the data from adenovirus vector trials would be invaluable to current or pending trials. Again, this is

an obvious area of need that has been woefully underfunded, if at all.

Finally, the question of the different roles to be played by big pharma, biotech, and the academic research community in planning and developing trials is unanswered. This is a difficult, amorphous issue to get a handle on. There is no likely monolithic model to follow for every trial, but underneath the outlines of this oft-edgy relationship lie issues of conflict of interest, resource allocation, and specific responsibilities for different phases and parts of preclinical and clinical studies.

Although many other specific problems were mentioned, most could be grouped into one of these five areas. Diagnosis is easy: the challenge is finding curative prescriptions.

#### THE CURRENT PROBLEMS CAN BE SOLVED

##### *Clinical Trial Training*

Too many independent investigators have tried to put together gene therapy clinical trials from scratch. The accumulated experience of those involved in any clinical trial should be harnessed. To that end, the meeting participants agreed that would-be clinical trial investigators should be trained by those most qualified to do so. The suggestion that the ASGT sponsor the development and implementation of 2- to 3-day workshops for its members that focus specifically on conduct of gene therapy clinical trials was roundly supported. Savio Woo, current president of ASGT, stated that membership education is a major goal of the Society and that ASGT would enthusiastically sponsor a joint subcommittee of its Education and Clinical Regulatory committees to push this forward. Not only would such a program elevate the quality of research being done, it would also help set high standards for conducting trials in all fields. It may be possible that, in addition to CMEs, a "certificate of training" could be issued by the ASGT as a sort of imprimatur that the holder had completed the course of training. The training would include regulatory issues with particular emphasis on the infrastructure necessary to provide adherence to the regulations.

##### *Public Education*

The panel agreed that no public forum is too small to be ignored. This means that gene therapy practitioners need to get involved locally, even to the point of offering to speak at rotary clubs. The difficulty is, of course, having the appropriate things to say and the resources to make the best presentation. Cabo participants suggested two ways to meet this need. The first is the organization of a "speakers bureau" of gene therapy researchers and practitioners across America, indeed worldwide, who would be willing to give such talks. The second is the development of a specific series of slides that could be used by these speakers, along with several talk "outlines" tailored to different levels of audience sophistication.

Again, this could be administered through the ASGT, with the support of biotech companies willing to provide "unrestricted" educational grants. It is important to remember that ASGT does not have limitless resources, and so educational efforts will depend heavily on the voluntary willingness of its members.

A couple of other ideas that floated but were not resolved included the possibility of a "mini-medical school" session on Capitol Hill for congressional staffers which deals with the current status of gene therapy as well as providing basic education about what is involved. It may also be possible to work with one of the public broadcasting programs (e.g., Discover or NOVA) to produce a documentary on gene therapy.

Much discussion centered on the role of the press. It is true that press coverage, especially recent articles, often sinks to the lowest level possible. However, that is no reason to refuse to speak with the press. Indeed, as one participant put it, "we have to talk until we are blue in the face" to provide an educational message about the reality, promise, and limitations of gene therapy. With a little more care and effort, we not only can slowly alter coverage but also can begin to undo the damage still being done by those gene therapy practitioners who persist in their overly optimistic assessments.

##### *Standardization*

The field needs reliable standards that are generally available. The question is who should take the lead on this? After much discussion it was decided that the best source would be the NCCR, who could put out an RFA for standardization techniques for each of the currently used vectors and appoint an oversight committee to evaluate both the applications and the resulting standards. It is clear that this oversight committee should include industry, academia, and FDA representatives to evaluate any proposed common use mechanisms, and there should be coordination with other interested parties or organizations to avoid duplication and/or contradictory outcomes. As this is an urgent need, it should be addressed as early as possible.

##### *Data Management*

The December RAC meeting demonstrated the willingness of researchers to share data from a variety of trials which were relevant to the topic of adenovectors. However, this mass of data is merely sitting in a large pile. The meeting participants agreed that the Office of Biotechnology Activities (OBA) should convene a group of scientists to quickly sift through the data and write a summary report that would be published in a suitable format, perhaps as a supplement to *Molecular Therapy*. The urgency of such action is obvious, particularly as many trials using adenovirus are already underway or planned for the near future. Similar work could be done for other topics of interest to gene therapy.

### *Academia and Industry*

The history of gene therapy is closely tied to the academic source from which modern molecular biology sprang. The strengths of this are most obvious in the creativity and excitement of daily new discoveries. The limitations are most keenly felt when the excitement of pushing ahead runs up against the hard reality of drug development. Somewhere in that interface is where many of the current problems can be found. The real problem is a lack of understanding by both parties of the particular motivations and goals of the other. Although there is no hard and fast model for interaction that will pertain in every case, there are a couple of things that could help clarify the respective roles of each.

Academicians need to be educated in the area of translational research, particularly in terms of the manufacturing issues that are faced by industry in developing new drugs. This may help smooth the way a bit as early studies will be designed with longer range goals in mind. A related issue is the relative lack of funding for studies of mechanism of action, so-called "gene pharmacology." By the time a pharmaceutical company commits to developing a promising drug, questions of mechanism take second place to the demands of drug development. Academicians not only could provide a great service by performing such studies, but they also could benefit from increased funding to do so. Industry, for its part, would benefit from a richer source of information in developing future products.

Of particular concern in this uncertain relationship is the issue of conflict of interest, particularly where the primary caregiver has a financial stake in the outcome of a trial. Realistically, a 4-day meeting in Cabo was not sufficient to resolve issues that have eaten up countless hours of government- or academia-sponsored meetings on this subject. It was the consensus of the group that this is an issue of great importance in its reality and perception. Since clinical investigators admit patients into trials under the belief of potential future applications

and many are involved in years of preclinical development for a study, it is difficult to erase all possible conflicts of interest. Added to these intangibles are potential economic benefits from patent or company involvement. Nevertheless, it was agreed that this issue must be taken up. To this end, Savio Woo reported that ASGT's Ethics Committee and Board of Directors have developed a policy statement on this critical issue, which appears in this issue of *Molecular Therapy* (1).

In short, it is clear that everyone involved in gene therapy needs to understand "the whole picture." No one PI can hope to oversee the entire process, but must see his or her particular protocol as a team effort that takes advantage of a lot of different expertise and technology.

#### SUMMARY: A PRESCRIPTION FOR THE FUTURE OF GENE THERAPY

It is a difficult time for gene therapy, but not a fatal one. In many ways, we are experiencing the growing pains of any young field of medicine. Granted, these are magnified for gene therapy, given the uneasy public reaction to the notion of genetic intervention and the intense media scrutiny following recent events. However, just as we have the opportunity to push this young field ahead, we also have the responsibility to adhere to current regulations and to follow tried and true models for developing what are, in essence, new drugs. Far from being a time to retreat, we need to stand up to the public and state clearly our successes and shortcomings, capitalizing on the first and working to change the second. Such meetings as the one in Cabo can only help by clarifying the issues at stake and respectfully recommending future directions to colleagues. The suggestions, outlined above, should be taken in that spirit.

#### REFERENCE

<sup>1</sup>Woo, S. (2000). Policy of the American Society of Gene Therapy on financial conflict of interest in clinical research. *Mol. Ther.* 1: 383-384.