



## a conversation with Dr. Philip Noguchi FDA's gene therapy expert

**DR. PHILIP NOGUCHI IS DIRECTOR, DIVISION OF CELLULAR AND GENE THERAPIES (DCGT), OFFICE OF THERAPEUTICS RESEARCH AND REVIEW, CENTER FOR BIOLOGICS EVALUATION AND RESEARCH, AT THE US FOOD AND DRUG ADMINISTRATION (FDA). DR. NOGUCHI HAS BEEN FOLLOWING GENE THERAPY PROGRESS IN HEMOPHILIA SINCE THE INITIAL WORKSHOP PUT ON BY NHF IN 1996. IN HIS CAPACITY AS DIRECTOR OF DCGT, NOGUCHI SERVES AS A RESOURCE TO SCIENTISTS IN BOTH ACADEMIA AND INDUSTRY WHO ARE DEVELOPING GENE THERAPY-BASED TREATMENTS.**

**Q WHAT DO YOU SEE AS THE MAJOR STUMBLING BLOCKS FOR GENE THERAPY PROTOCOLS IN 2001?**

► For any new product, the finances and getting appropriate academic and pharmaceutical companies interested are going to be issues. While we are seeing a steady number of gene therapy Investigational New Drug applications (INDs) coming in, some major companies are now starting to admit that they may not be quite as interested as they were before. I don't know exactly how many potential patients there are in hemophilia, but clearly the traditional pharmaceutical model of having to have a certain market in order to justify developing for that particular

BY JUDY BERLFEIN

disease is not the correct one for genetic diseases. Hoffman-La Roche and Schering took a little different approach with interferon that may be needed for gene therapy. Rather than saying the disease that we're studying is not big enough, they had a product for which they were studying activity in a variety of diseases. Another area where there is obviously a bit of skittishness regarding gene therapy is among people who are wondering about what happened in Philadelphia with Jesse Gelsinger. (See sidebar on page 15).

## Q WERE THERE SPECIFIC HURDLES FOR STARTING HEMOPHILIA GENE THERAPY CLINICAL STUDIES?

► I think the very first hurdle that has already been overcome was at the first NHF hemophilia gene therapy workshop before there were any gene therapy trials and there was no inkling that such things would be seen within one or two decades. The good news is that the clinical trials have started. We're now at a point where there will be some reluctance to do things that have already been done. The hurdle is not so much from the FDA. If somebody else wanted to do an intramuscular adeno-associated viral (AAV) trial, there would be nothing, as far as FDA is concerned, to prevent him or her from doing that. The specific hurdle right now is going to be the realization that the supply of volunteers for these experiments is rather small and the approaches that need to be looked at are quite broad. It's that balance of diversity that needs to be driven and assessed by the hemophilia community. What are the next steps to take? Should the muscle trial be completed or should subjects be saved for future trials? You're already starting to see those kinds of tradeoffs being discussed. Because the first experiments have been started, the bar has been set higher. There is probably going to be little enthusiasm by the com-



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munity for any trials that wouldn't begin to demonstrate some level of factor expression. The expectations have been set higher.

## Q DO YOU THINK HEMOPHILIA WILL BE CURED BY GENE THERAPY?

► It is FDA's hope that hemophilia will be cured. The reason FDA is much more conservative in estimating times is because we see not just hemophilia, but all diseases being studied. By and large, we know that most products that are tried in any disease, let alone hemophilia, are not going to be what ultimately is licensed or approved as a drug. We review primarily on the safety of a product as it is being used in a clinical indication and ultimately rule on its effectiveness. But we try to not get too much into the scientific rationale. There needs to be some

rationale. But the quality of the science and the quality of the effect is really impossible to extrapolate to the human experience. That's what clinical trials are all about. And what we find is that those things that work in animals much of the time are completely unfounded as a therapy in humans. So, as an equal-opportunity consumer protection agency, we will take everything that comes in the door. We will make sure it's as safe as we can make it by interacting with as many people as we need to get the best expertise. We will not predict on the basis of animal studies which treatment has a better or worse chance of success. We can make predictions, but often we'll be wrong.

## Q HOW DOES FDA MAKE DECISIONS REGARDING SAFETY WHEN LITTLE INFORMATION IS AVAILABLE?

► We try to evaluate animal data in which the toxicity of the vector is addressed. Hepatitis C (HCV) is very problematic because there aren't any easy animal models or *in vitro* models. We do the best we can with available data. We make the sponsors do as many of the studies as they can; that's where a bit of negotiation does come into play. For HCV, we are exploring the possibility of using chimps that are infected with the virus; however, they don't recapitulate human disease, so it may not be a perfect model.

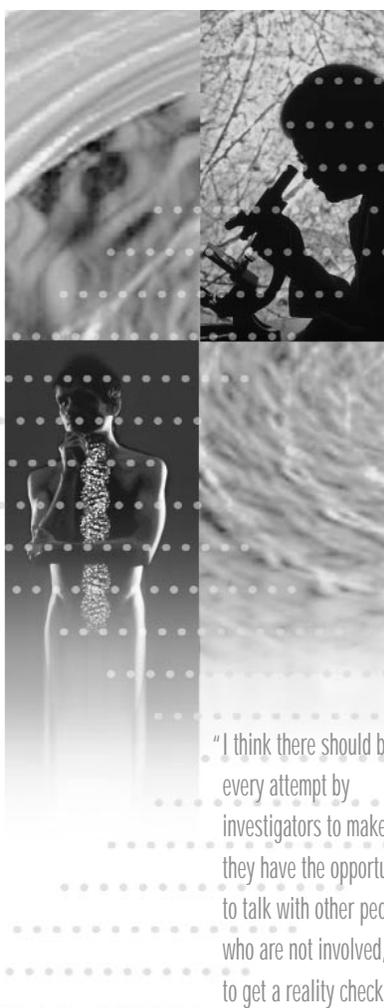
In the end, there is an element of decision making that is based on as much as we know at that time. Sometimes we go ahead even when we don't know all the answers. For example, reasonable results in chimps may require 10- or 20-year follow-up. Do we want to hold up trials and say vectors cannot be administered to the liver until we have answers in chimps? It may not make good scientific or policy sense to wait for the results because new models may be coming out. In the meantime, with the full understanding and collaboration of human ►

▶ subjects, we think it is worth taking the risks to move forward in a cautious fashion.

**Q WHAT QUESTIONS SHOULD PATIENTS ASK IF THEY ARE CONSIDERING ENROLLING IN A GENE THERAPY STUDY?**

- ▶ Patients should ask several questions (these are not restricted to gene therapy).
  - Where can I get another opinion—one that is independent, unbiased?
  - Who will be my investigator and how much information will he or she share with me?
  - What are the investigator's clinical monitoring plans?
  - How will the investigator decide that the trial is proceeding as expected?
  - What will the investigator do if one of the subjects develops a condition that is a little bit unusual? How is the investigator going to handle it?
  - Is this a treatment or is this experimental? How experimental? Is this gene transfer still in early development or more advanced? Should I expect clinical benefit?

The subjects need to feel that they can ask questions and not be treated in a paternalistic fashion. I don't know if this happens in hemophilia or any other trials of gene therapy. My expectation is that, in general, it would be a fairly open process. But it doesn't hurt for the volunteer to establish up front what he or she is going to know. The level of importance of information-sharing needs to be elevated to a ritual concept; the informed consent process isn't even close to what we're talking about. We're talking about a commitment by the volunteer and the investigator to join together in this journey that is unknown. As a patient who is a human subject in a trial, there are three outcomes to



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be aware of: the volunteer will get better, stay the same or get worse. Each one of those could be related or unrelated to the drug. We do know that it is very, very likely if improvement does occur, that it is not because of the drug; it may be because the subject is receiving better care or he or she is taking better care of him or herself. It is like a marriage in some ways. Anything is possible, but one needs to be prepared for the worst possible outcome until "death do us part". Death occurs very rarely. However, if there is no acknowledgment that the worst can happen and one is only looking for the good things, one has false expectations. Only when FDA sees objective improvement from a treatment is it approved for marketing.

**Q WHAT IMPACT HAS THE RECENT GENE THERAPY DEATH OF JESSE GELSINGER HAD ON REVIEW AND CONDUCT OF GENE THERAPY AND CLINICAL STUDIES?**

▶ Where the death had the most impact was in the conduct of clinical trials. It has refocused everyone involved in clinical trials on those things we knew about, but may not have focused on in a consistent manner. For example, part of the oversight of clinical trials is designed to be done by a local institutional review board (IRB). That's a fine idea in concept, but the reality for IRB (just like many tasks by done by FDA) is that it is an unfunded mandate by and large. If you're going to have IRB oversight of some nature, you need funding for that. If you only had to review a few trials, it's reasonable to expect participation on a voluntary basis. But there are approximately 35,000 clinical trials going on in the country at any one time. Some institutions may have four or five IRBs, each of which are reviewing hundreds of trials per year. The death has forced us to look at the IRB situation by the academic institutions, the new Office of Human Research Protections (OHRP) and the National Bioethics Advisory Commission (NBAC).

The second aspect of this is clinical monitoring. We are requiring all gene transfer INDs to provide a description of the clinical monitoring plan. It is already a requirement in the regulations, but typically we had not required it to be submitted with the IND.

**Q DO YOU THINK CLINICAL TRIAL REVIEW BY THE NATIONAL INSTITUTES OF HEALTH (NIH), RECOMBINANT DNA ADVISORY COMMITTEE (RAC) AND FDA IS MORE EFFICIENT AND COORDINATED NOW?**

▶ Yes, it is. There have been some ups and downs. ▶▶ TO | 34

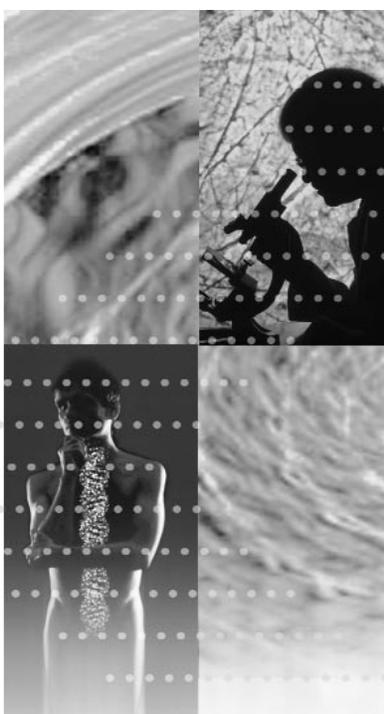
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► But we now have formal written procedures in place on how we keep the Office of Biotechnology Activities (OBA) at NIH up-to-date. OBA keeps RAC informed, as RAC is an advisory committee to NIH. We're continuing to discuss the best way to look at adverse events and the best way to coordinate adverse event reporting. Are the reports going to each agency the same? Sometimes yes, sometimes no. How can we address that? NIH talks about investigators, while FDA talks about sponsors. You may have many investigators under one sponsor. There is this difference in the constituency. Yes, working relationships between the different groups are more efficient and more coordinated. Is it ideal? No, we have a lot of work to do.

**Q ARE THERE INHERENT CONFLICTS FOR CLINICIANS WHO CARE FOR A PATIENT POPULATION, SUCH AS HEMOPHILIA TREATMENT CENTER (HTC) PHYSICIANS, WHO ALSO RUN CLINICAL TRIALS IN THAT POPULATION?**

► That is an extremely important and elusive issue to address. As a physician practicing medicine, your duty is to treat that patient to the best of your ability as that patient progresses. That is your mandate. When you enter that patient in a clinical trial, he or she becomes a human subject in an experiment. The person has not changed, but what that person represents is different. Your obligation, as an investigator, is very complicated; it is to take care of that patient who is under your care in the context of that clinical trial.

No one develops a product thinking it is going to do worse than current therapy. Everyone has, at best, just a neutral opinion. Most of the time you really think it's going to work. That will bias your actions in some fashion. The best of the clinical investigators will try



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to be as objective as they can. But, quite frankly, the stance taken by the American Society of Gene Therapy (ASGT) is a very progressive one and one that is not universally supported. The position is that, if you have any part in development or stock in a company, you cannot participate as investigator in a clinical trial. You develop the product or you do the clinical trial; you do not do both. Although it is likely FDA would not take that position, we think it is an admirable position.

**Q DO YOU THINK THE LEVEL OF TRAINING AND CERTIFICATION IS SUFFICIENT FOR CLINICAL INVESTIGATORS?**

► Our feeling is, while there may be clinical investigators who know all

the requirements in the area of gene therapy, there are many new investigators. There hasn't really been a well-organized agreement concerning training and certification. The pharmaceutical industry does have its own programs for training and certification, but it has not been on the radar screen of many people. From the Jesse Gelsinger case, there is now an awareness that, if you are an investigator in a clinical trial, you really have to know a lot of things. We need to examine better ways of doing that. ASGT is offering a training course on conduct of gene therapy clinical trials for its members, co-hosted by NIH, FDA and OHRP. We have speakers from all areas that will take part. At the end of the course, ASGT will issue a certificate to those who go through the entire process. This is the first time we've tried it. We think it's a good start.

One thing investigators can do is to be more open to discussion about what they're doing. They may want to have a colleague who is not involved in the trial occasionally accompany them and say, "Okay, let me show you what I'm doing," and go through it and later say, "What do you think? Did you see anything I might have forgotten or that you would have done differently?" Different people have different strengths. The first time you do a clinical study and you inject 1,013 particles over a two-minute course, that's a fairly daunting thing. I think there should be every attempt by investigators to make sure they have the opportunity to talk with other people who are not involved, just to get a reality check. A lot of what we are talking about is not medical science or rocket science; it's just common sense. If it's not written down, it didn't happen. The most careful scientists write things down as they do them. Especially if you make a mistake that leads to a patient's death. If you don't document it, no one can learn from the mistake. ☺