An Unparalleled Engine for Discovery and Clinical Introduction: The Clinical and Translational Science Awards and Gene Therapy

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GENE THERAPY has taken longer than any of us had hoped to come to clinical utility. Its promise is only now beginning to be fulfilled. Improvements in vectors and sufficient duration of follow-up now indicate that for some indications, such as severe combined immune deficiency, Leber congenital amaurosis, and hemophilia B, gene therapy is effective (Thrasher *et al.*, 2006; Silver and Flotte, 2008; Kohn, 2010; Kaiser, 2011; Nathwani *et al.*, 2011; Ponder, 2011; Jacobson *et al.*, 2012). Other diseases, both single gene and multigene, may also yield to this therapeutic approach. But gene therapy is now at the preclinical stage for most indications, or just coming to phase I and phase IIa studies in humans. At this stage, the field will need studies of biomarkers, preclinical animal testing, ethical considerations, and first-in-human studies of the gene therapy reagents compliant with federal regulations, with careful follow-up studies for life. The intensity and lifelong duration of the follow-up studies required, if not the number of subjects necessary for these studies, will require informatics, data capture, and data storage. Development of novel therapeutic approaches and their testing in appropriate patient populations will require the resources now assigned to the Clinical and Translational Science Award (CTSA) program. But is the program ready for this challenge?

The CTSA program

The CTSA program, until now awarded from the National Center for Research Resources (NCRR), after five competitions reached its intended complement of 60 sites. This program was designed to collect the infrastructure support to clinical and translational research for a given institution, as well as its training functions, in a single comprehensive program, by subsuming the General Clinical Research Centers (GCRCs) as well as training grants at the predoctoral (T32) and postgraduate levels (K12), and adding components of regulatory support, bioinformatics, translational technologies resources, and community engagement. The CTSA was intended to be the hub for patient-based research in academic medical centers, and to provide this support to all investi-

gators in the health professions (not just medical schools) as well as to collaborating hospitals and clinics. This extremely important program has, even in its early years, notched important successes in bringing together local institutions that had operated in isolation for many years, streamlined processes of clinical research, and initiated national collaborations for studies requiring rapid enrollment, education, and informatics. In addition, the CTSA program inspired institutions to invest in infrastructure for clinical and translational research. New buildings, informatics support beyond electronic health records, regulatory support systems, and pilot funding, as well as the institutional commitments required to accept T32 and K12 funding through the CTSA (cap gap, research project support, additional tuition support, and the mechanics of operating institution-wide competition for positions) have all been committed to enhance clinical and translational research in CTSA and other competing institutions. This program is clearly intended to be the main vehicle for National Institutes of Health (NIH) investments in the infrastructure required for gene therapy.

The CTSA program replaced the GCRC program entirely, and added requirements for community engagement, a pilot program, regulatory knowledge and support, bioinformatics, and translational technology support. The original intent was to continue funding to institutions that folded in GCRC and education programs, and then to add funds for the newly required components. However, after the first “class” of 12 CTSA received funding in 2006, the NCRR reconstructed the funding formula in order to accommodate all 60 intended programs within a budget of \$500 million. The new funding formula provided 25 to 50% less than the amount originally planned to each institution, depending on the composition of existing programs at the institution, beginning with the programs funded in 2007. As the class of 2006 came up for renewal, the new formula was applied to them as well, so all programs are now operating under the reduced funding model. Budget constraint, combined with an expanded mission, has necessitated cost efficiencies, reduction of services, and/or cost recovery plans for services previously provided without charge.

New Services Included in CTSA Programs

Some of the new services included in CTSA programs are highly relevant to progress in gene therapy. For example, explicit funding for regulatory knowledge and support, subject recruitment, informatics, bioethics, and translational technologies may all support gene transfer protocols. Regulatory requirements for gene therapy are considerable, and assistance to investigators is valuable. Identifying the most suitable subjects for gene therapy by bioinformatics means and characterizing the subjects by genomic, proteomic, metabolomic, or other biomarkers (which might also follow progress), may well allow construction of efficient gene transfer clinical protocols. Maintaining the data on the subjects for gene therapy protocols, for life, will require informatics tools. The consolidation of clinical and translational research infrastructure into a single program—a one-stop shop—at each of 60 awardee institutions has also resulted in the opportunity for better coordinated assistance to investigators, particularly the inexperienced. Many programs have established experienced navigators, research managers, or concierges whose mission it is to conduct the investigator through the maze of requirements, and to facilitate access to services for clinical/translational projects. Of course, the degree of assistance that is provided depends on the expertise of the navigator, and the depth of expertise in the facilities they can access. For example, expertise in U.S. Food and Drug Administration regulations, required for most gene therapy protocols, is highly variable from institution to institution.

An area especially relevant to gene therapy is the public-private partnerships that have come to be expected in CTSA programs. In an era of resource constraint as we are facing now, such partnerships will be crucial in advancing discoveries to patient care. The CTSA sites are especially well suited for such partnerships for gene therapy, because of the broad range of exquisitely detailed investigations that are necessary to implement viral (and nonviral) gene therapy safely—identification of insertion sites, detection of antibody to vector, establishment of purity of the vector solution, and so on in the laboratory, but also imaging and marker development and monitoring on the clinical side.

One of the virtues of the CTSA program is that it is disease neutral. Resources are provided that are not restricted to a particular disease or organ system. For gene therapy, this is important, because it is often the vector that drives creativity, and an appropriate disease target emerges only as the vector is perfected. The regulatory requirements are similar whatever the organ system. On the other hand, access to appropriate research subjects is critical. The CTSA programs have created both national and local research subject registries. Despite their portfolio that is agnostic to disease, the CTSA programs are now collaborating with some of the categorical NIH institutes to create clinical trials networks that may be ideal for rare diseases, as may be the substrate for some gene therapy protocols.

However, other aspects of the revamped CTSA programs may not be as favorable for gene therapy protocols. Studies that in the past may have been supported entirely by funds from the GCRC, including full bed costs, laboratory costs, and enhanced nursing costs, may now have to be charged back in part to the research protocols. Although protocol assistance, ethics consultation, regulatory support, and informatics as-

sistance may now be provided, many out-of-pocket costs of the clinical studies themselves now must be borne by project funds. In addition, most clinical research units have been forced to become quite strict about applying full charges for industry-supported protocols, which may be difficult for struggling biotechnology companies to bear. Other changes in the GCRC model have occurred in many of the CTSA programs. In most institutions, in the past, GCRCs were housed in a single defined unit, some of which provided such niceties as negative pressure rooms to reduce escape of vector administered to the lungs, or laboratories for vector or tracking drug preparation positioned close to the research beds. For some CTSA programs, cost reductions have demanded that inpatient research support be provided on the scatter bed model, that is, in nursing units devoted to clinical care, with supplemental research nursing support for the protocol provided through the CTSA, separate from the clinical nursing. Moreover, in the later CTSA competitions, patient care resources were not a requirement, so some CTSA sites do not support GCRC-like units at all.

Variability Among CTSA Sites

There is enormous variability among CTSA sites, in the services they offer and the relative emphasis that they place on the various services. One need only examine the wide range of NIH funding for CTSA programs, from \$3.9 million to \$24 million per year, to realize that the ability to support any particular service in any given CTSA site will vary greatly. These awards exist at institutions that, including all collaborators, garner from \$32 million to more than \$1 billion per year in NIH funding, so the complementary resources are also not uniform. Institutional commitments differ, too, so the infrastructure capacity derived from other sources also differs among sites. Some sites will be able to provide the many layers of service required for gene therapy protocols, and some simply will not be able to support all of them. It may be that gene therapy protocols will congregate at especially hospitable sites. Such sites would probably provide extensive assistance in compliance with federal and local regulations, an inpatient clinical research unit, possibly GMP laboratories in which the vectors can be prepared or hospital rooms that could contain the vector if required, informatics support for longitudinal monitoring of subjects, and support for the myriad laboratory and imaging tests that will be conducted in phase I to verify safety, and in phase II to demonstrate efficacy.

As the CTSA network has evolved, there has been increasing recognition of nonuniformity of resources and of purpose, and the NIH vision has sharpened to admit that the different sites will have different strengths, and not all sites will provide all services. However, the network as a whole should have all, or nearly all, services available, as well as the capacity to develop needed new tools. Some specialized resources may be available at only a few sites, but the NIH vision may be that resources can be accessed from any site. However, the issues of the need for return on institutional investment in highly specialized resources vis-à-vis the national good have not fully been explored, and the mechanisms by which this might occur have not been developed. Also, such a model may not be maximally convenient for investigators, particularly if the resources

they require exist only at remote sites. Nevertheless, the extraordinary breadth of expertise subsumed by the 60 CTSA sites is remarkable, and collaborative efforts have already begun to take shape.

Evolution of the CTSA Program

The CTSA model continues to evolve. The challenges to the NIH and other federal budgets have caused the NIH and the community to reconsider all funding mechanisms in order to maintain the support of research project grants. In these difficult times, large grants like the CTSA seem tempting targets to bleed in support of other, smaller grant mechanisms. Such a maneuver would impact negatively clinical research at all levels, including research relevant to gene therapy. For example, the clinical research unit at the author's institution supports 23% of the R01 grants awarded to the school of medicine, and this support would inevitably be reduced if there were across-the-board cuts to CTSA. Indeed, one of the mechanisms to free extra dollars for research project grants that has already applied for fiscal year 2012, reduction of the NIH salary cap to executive level 2 from executive level 1, impacts physician scientists disproportionately. Institutions, now forced to support a larger portion of salary for highly compensated physicians, will think twice about freeing physician time for research, even if it is partially compensated by federal salary support, for their other sources of funding are under great pressure as well.

As this commentary is being written, NCCR is being de-commissioned and a new center, the National Center for Advancing Translational Sciences (NCATS) is being established, with the CTSA constituting the bulk of the initial budget. It is unclear whether the focus of NCATS on drug development will extend to the CTSA and shift the emphasis from broad-based support of translational research at all levels to development and human testing of novel drugs, including, presumably, genes as drugs. If the focus sharpens in this way without reduction in total funding, opportunities for support of gene therapy may increase. If the focus sharpens, but the budget is cut, or if broad-based support of translational research is expected at the same budget, then the situation may be the same as it is at present. If the CTSA budgets are cut, but with expectations maintained as they are now, for a broad portfolio of support for translational research, then all aspects of patient-based research will suffer. So, at this point in time, even setting aside the

vagaries of the NIH budget and the commitment of Congress to innovation in biomedical research, and setting aside the looming challenges to the budgets of academic medical centers in the next few years, it is difficult to predict how well the CTSA will accommodate novel and complex therapies such as gene therapy in the future. However, no other NIH mechanisms provide the infrastructure support for development of complex and novel treatments. The combined engine of innovation and clinical introduction represented by the CTSA as a group is unparalleled.

Author Disclosure

No competing financial interests exist.

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