IMMUNOLOGY

Ten Years of the Immune Tolerance Network: An Integrated Clinical Research Organization

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The U.S. National Institutes of Health Roadmap and the U.S. Food and Drug Administration's Critical Path Initiative have endorsed the establishment of large academic clinical research networks as part of the solution to the growing divide between increased R&D spending and the lagging number of new drugs making it to market. Clearly, the role of these networks as translational science incubators that complement industry-sponsored programs is laudable and much-needed. However, the path to success for such organizations is less clear. Here, drawing on the experiences of the Immune Tolerance Network, a multidisciplinary clinical research network founded in 1999, we discuss some of the barriers inherent in developing such consortia and offer firsthand insight into the planning, resources, and organizational infrastructure required for a successful research program.

INTRODUCTION

Despite a dramatic rise in investments in clinical drug development, the past decade witnessed a progressive decline in first-in-class medicines making it to the bedside (*1*). The cost of discovering and developing a new first-in-class drug is now estimated to be more than $1 billion (*2*). These alarming trends have prompted many pharmaceutical companies to focus on second-generation versions of already-validated drugs rather than on new drug discovery. The acquisition of small biotechnology firms with novel small-molecule leads and libraries has slowed, and although this pipeline-purchasing approach may yield some successes in a somewhat abbreviated time span, it also may represent a focus on generic and "me-too" drugs, rather than "me-first" therapeutics. This drug-discovery climate is discouraging in light of the extraordinary opportunities presented by genome era–driven basic research discoveries. In response, wide-ranging efforts such as the U.S. National Institutes of Health (NIH) Roadmap for Medical Research and the U.S. Food and Drug Administration's (FDA's) Critical Path Initiative—both designed to facilitate the discovery and development of innovative medical treatments for devastating diseases—have begun to address this problem in part by establishing large integrated research networks.

Because the pharmaceutical industry itself rarely builds enduring networks, operating primarily on a (clinical) trial-by-trial basis, the creation of stable academic institution–led networks is needed to complement industry-led efforts and accelerate progress through the clinical development cycle. These networks would benefit from economies of scale and industry-style operational efficiencies, while promoting biomarker research that helps to illuminate disease mechanisms, decipher the functions and targets of therapeutic agents, and enable patient stratification (for clinical trials) and treatment monitoring in ways not previously achievable. However, although the concept is laudable, implementation has been challenging.

In this essay, we describe the Immune Tolerance Network (ITN) (http://www.immunetolerance.org), an academic consortium of basic scientists and clinical and translational researchers that has established just such a system, with a focus on integrated multidisciplinary team–oriented research. We believe that the ITN's efforts have been successful in developing a new paradigm for bridging traditional research establishments, while broadening our understanding of disease processes and promoting changes in patient care. The experiences of the ITN may be instructive in the planning and implementation of other similar entities.

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THE ITN

In 1999, the National Institutes of Allergy and Infectious Diseases (NIAID), the Juvenile Diabetes Research Foundation (JDRF), and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), partnered to create the ITN with the vision that meaningful progress can be made when a team of dedicated researchers, physicians, and government and industry professionals assembles to tackle difficult and diverse clinical problems. At the time, a wealth of preclinical data from animal disease models suggested that immune system–mediated diseases (such as autoimmune diseases, transplant rejection, allergies, and asthma) could be treated with new classes of drugs designed to induce immunological tolerance, so that short therapeutic interventions could lead to long-term drug-free existence. With the preclinical pipeline growing substantially and a broad spectrum of diseases to target, tolerance modulators represented an underexplored therapeutic opportunity. However, because the pharmaceutical industry did not widely pursue this "Holy Grail" of academic immunology, the NIAID leadership sought to turn this fertile preclinical environment into a robust clinical pipeline. The question before the NIAID leadership in the late 1990s is similar to the one now faced by myriad subfields of biomedical research: How can scientists translate rich and intricate bodies of basic and preclinical research into new therapeutic agents and creative approaches to fighting disease?

SOME ASSEMBLY REQUIRED

The concepts behind the ITN grew out of consultations with the immunology research community, representatives from biotechnology and the pharmaceutical industry, professional society members, and patient advocacy groups. First, to enable broad implementation of new concepts and developments across multiple disease areas, investigators from the related but traditionally separate disease areas of autoimmunity, transplantation, and allergy/asthma needed to be assembled. Second, the solicitation and encouragement of industry participation would be a key to success. Third, many of the agents likely to be tested in clinical trials were just emerging from the discovery pipeline and, in some cases, there was a dearth of preclinical and human mechanistic data to

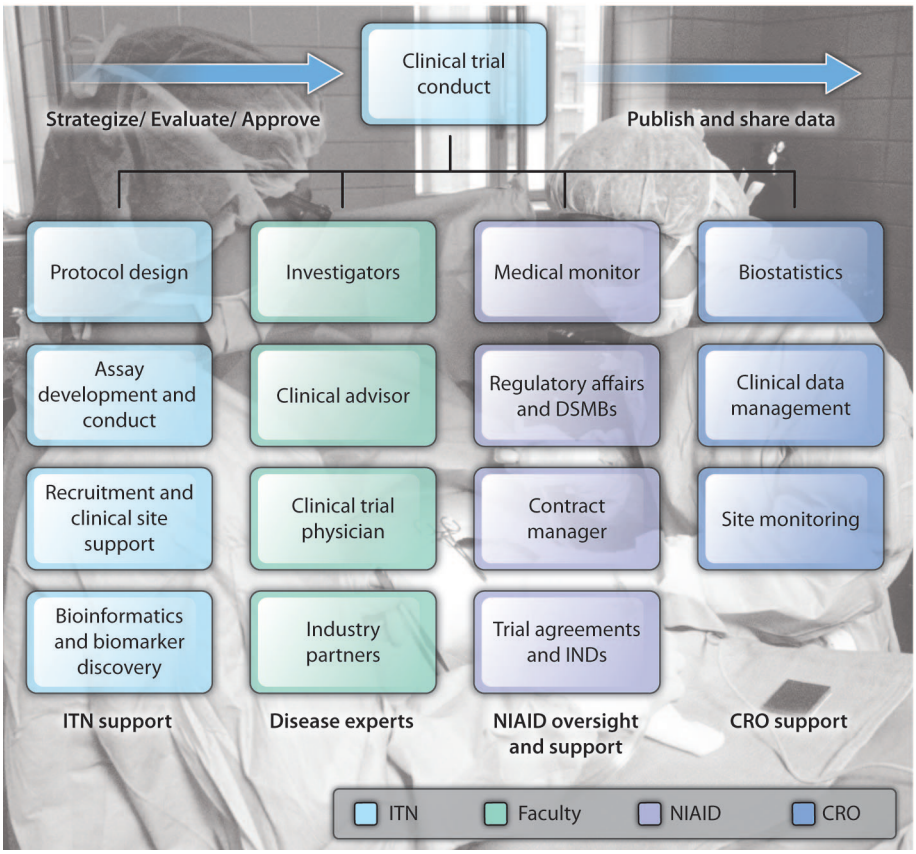

Fig. 1. The collaborative infrastructure for ITN-conducted clinical trials. The development, implementation, followup, and analysis of each ITN clinical trial are achieved through a wide-ranging collaboration that includes specialized ITN staff, NIAID regulatory and support staff, dedicated contract research organization (CRO) staff, and academic investigators and advisors who guide the study.

guide clinical trials. Finally, the ITN would incorporate studies on biomarkers, which could ultimately be used to guide individualized therapy, predict treatment success and failure, establish surrogate therapeutic endpoints, and direct second-generation drug development. Thus, the ITN was founded as an integrated clinical research enterprise in which "the bedside is the bench." This view emphasizes knowledge generation through mechanistic assays and biomarker discovery, in addition to the traditional clinical trial endpoints of safety and efficacy.

The ITN's mission is to design and conduct difficult but high-impact clinical studies by leveraging the capabilities of academic research. To this end, the ITN seeks to bridge the best of the academic and industry worlds by emphasizing the strengths of each: the intellectual creativity and focus on mechanism-based research offered by academia and the innovation, efficiency, and unyielding focus on drug development that defines industry. The ITN, NIAID, and Rho (a contract research organization) employ more than 125 people who perform a variety of critical functions for ITN research, including (i) the solicitation and review of a wide range of proposals generated by the research community at large; (ii) strategic planning, through an internal steering committee of Ph.D. and M.D. researchers who are not members of the teams that conduct ITN clinical trials; (iii) development of investigational new drug applications; (iv) oversight of the conduct and regulatory aspects of clinical trials; and (v) the application of sophisticated biomarker and mechanistic assays to augment clinical results by increasing our understanding of disease pathogenesis and drug mechanisms of action (Fig. 1). After a decade in existence, the ITN counts many accomplishments (Table 1), including multiple publications in high-profile journals, clinical trial results that are likely to improve patient care, and new insights into the basis of tolerance in transplant recipients who are free of immune-suppressive drugs.

LESSONS IN NETWORK BUILDING

One major difference between the ITN and other similar consortia is that the ITN is funded through a contract to a single institution (the University of California, San Francisco). In many networks, a relatively small number and fixed set of individual institutions have a seat at the table, and some such groups may lack incentives to pursue studies proposed by researchers not initially affiliated with the network. In contrast, the ITN uses a highly interactive and inclusive approach that ensures open access to a highly collaborative environment. In this framework, the ITN can distribute funds to other institutions on the basis of the strength and ingenuity of their ideas and their clinical trial proposals. In fact, separation of the evaluating committee from the "grantees" is one way that the ITN remains agile and able to focus on high-impact studies that will advance the field.

Although the mission and founding principles of the ITN remain the driving force behind the organization, the ITN has also evolved to include sophisticated capabilities beyond those initially envisioned. Examples include the development of a particularly strong bioinformatics infrastructure; creation of an extensive, high-quality, biobank and sample-tracking system; and establishment of many centralized resources for mechanistic studies. Given the ever-changing nature of science and medicine, this ability to adapt is perhaps the most important lesson to be gained from the ITN experience. It is, in fact, a testament to the strong commitment and collaborative relationship between the ITN and its sponsoring agencies, which have offered the consistent support and insight

Table 1. The ITN by the numbers.

18 centralized, standardized core assay facilities
28 clinical trials completed or in progress; 8 in development; 6 in the pipeline
85 published manuscripts, 3 published in the *New England Journal of Medicine*; 132 meeting presentations
125+ full-time employees dedicated to the ITN
257 concept proposals received since 1999
167 active clinical sites
5865+ people participated in ITN trials
25,000+ assays performed by ITN cores
370,000+ clinical specimens stored in the ITN repository

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needed to meet contemporary challenges with fresh approaches.

The value proposition. A common concern within academic circles about clinical research networks is that they expend large amounts of money that could otherwise be used for basic research. The oft-repeated battle cry is "Let the pharmaceutical industry carry the freight for clinical application!" And indeed, there is an element of truth in this view. There is no doubt that the infrastructure behind industry-supported clinical trials is highly sophisticated and efficient, and the private sector is generally able to plan and conduct trials faster and at lower costs than most academic networks can realistically hope to achieve. But this truth misses the point. Academic research networks were never meant to simply duplicate the existing industry-supported infrastructure. Instead, they are a critical element of our national health research enterprise that provides a means of addressing otherwise unmet needs, such as long-term observational, epidemiological, and large-scale genomic, proteomic, and epigenetic investigations; prevention and intervention studies based on lifestyle and social factors; and rare, orphan, and neglected diseases, to name just a few. Herein lies the key value proposition of a multidimensional clinical research network: the necessary services it performs. The ITN experience and the current emphasis on translational medicine in a variety of areas argue strongly for the value of human mechanistic data. With the failure of many animal models to accurately predict human clinical responses, the practical value of a richer mechanistic understanding has never seemed clearer. Integrated mechanistic studies should enable the identification of new clinical phenotypes, the stratification of clinical research cohorts, and the discovery of new biomarkers and drug targets. Collectively, these efforts will eventually streamline drug development and licensure, and may aid in predicting late-stage drug failures earlier in the development process. By establishing an infrastructure that allows investigators to conceive and carry out these integrated mechanistic investigations, clinical research networks provide a value-added service that acts as a bridge between academic and industry goals.

But it is no simple task to create an academic enterprise that can challenge dogma and rapidly and efficiently test new ideas, while at the same time working with industrial partners who often have the most interesting therapeutics, yet at times differing agendas. Very likely, the most difficult challenge any network will need to overcome lies in establishing a shared vision and values that are at once compatible with both the needs and goals of academics and the expectations of industry.

Challenges to working within academia. In academia, access to research funding and academic recognition are generally predicated on individual accomplishment. In contrast, the network approach involves teamwork and an element of self-sacrifice for the good of the enterprise. A collaborative research network must always work to recruit and maintain exceptional individuals. The ITN has addressed this by offering opportunities to participate on several different levels: through leadership opportunities, serving on advisory committees and, most importantly, serving as principal investigators of investigator-initiated clinical trials. However, substantial challenges remain. Performing complex clinical trials within single academic centers is problematic, and multisite studies entail many organizational challenges. In addition, the traditional silos of academia, industry, and government are not conducive to the translation of biomedical research. Moreover, the ITN's practice of working with investigators to improve on attractive, but yet to be fully developed clinical trial concepts stands in contrast to the binary decisions typical of NIH peer review. In some respects, the ITN deliberations and decision-making practices may resemble the way industry works with scientific advisory boards and investigator teams, done in an open, inclusive, and transparent environment.

Challenges to working with industry. An academic clinical research network can offer potential industry partners the refinement and validation of concepts investigated by leading academic scientists and opportunities for pharmaceutical industry scientists to publish along with their academic peers. For some biotech companies, partnership with the ITN provides access to regulatory expertise and independent recognition. An infrastructure that facilitates integrated mechanistic studies also furnishes industry with additional data that may ultimately lower a company's exposure to safety risks and be valuable within the investment community. In fact, the ITN assay infrastructure is increasingly behind the motivation of companies to partner with the ITN.

Yet even with sufficient interest, finalizing a partnership is difficult. Given the growing costs of bringing a new agent to market, companies are understandably risk-averse and steer their candidate drugs through tightly controlled, but expensive, development programs. Naturally, most are cool to the notion of testing an unapproved drug in a secondary indication for fear of adverse events that could impose regulatory delays or influence licensure in the primary indication. Nonetheless, the ITN's relationships with large pharmaceutical companies continue to grow, seeded initially by off-label studies of already-approved agents, but more recently by an increased interest in research that uses unlicensed agents and first-in-human studies for rare and neglected diseases. In other cases, the ITN has partnered with biotechnology firms; because these companies have narrower pipelines, the prospect of additional licensed indications and access to NIH resources may be of greater immediate value to the company and enhance its ability to attract private-sector funding.

Not surprisingly, intellectual property (IP) issues are often the greatest perceived barrier to industry partnerships. Whereas industry has an obvious inherent interest in safeguarding and growing the value of its intellectual property, academia has traditionally relied to a great extent on open communication, peer review, and academic freedom. However, the new reality is that academic institutions have no less interest in IP, and thus there is more common ground between academic institutions and industry than there has been in the past. So is there really a problem? In general, IP issues centered around inventions have already been settled by the Bayh-Dole Act, which was passed in 1980 for the purpose of ensuring that universities, small businesses, and nonprofit institutions could retain control of inventions and other IP resulting from federally funded research.

Funding and infrastructure. One key to successful partnerships is to identify complementarities and capitalize on the strengths of the respective partners. For the ITN, this has meant an integrated approach, so that the peer review, protocol development, and clinical operations are handled jointly by NIAID and the ITN, with support from contract research organizations. The regulatory elements are managed by NIAID with input from the ITN and outside advisors, and ITN clinical trials are monitored by NIAID Data and Safety Monitoring Boards. Finally, site monitoring and clinical data operations

are performed by a contract research organization, currently Rho, which is under contract to NIAID. The number and location of clinical sites are selected as per the needs of each trial, whereas mechanistic assay cores are located at leading academic and industry laboratories but coordinated centrally. This organizational structure has allowed the ITN to maintain high-quality assay data across widely distributed clinical sites and trials of various indications with a high degree of protocol consistency, while using standardized shipping and handling protocols and rigorous quality-assurance and quality-control procedures, as well as performing frequent validation. All of these activities are coordinated through this centralized support infrastructure. Similarly, the vast amounts of data generated by these assays (ITN cores have performed >25,000 individual assays and banked more than 370,000 clinical specimens) require extensive specimen tracking and supporting bioinformatics infrastructures, as well as novel analysis methods capable of deriving meaning from merged clinical and mechanistic data sets. This last area remains a challenge, because new bioinformatics tools and computational approaches are needed to bridge diverse, high-density data sets and clinical outcomes. Finally, relatively stable funding has enabled the program to take a long-range view on trial size and duration, which is important for networks that study chronic, relapsing, remitting diseases.

Metrics for success. Because the role of clinical research networks such as the ITN is distinct from that of private industry, traditional measures of success may not apply. According to the mission of the ITN, assessment should be based on whether (i) trials are being performed that would otherwise not be undertaken, (ii) the results of the trials have noticeable impacts on drug development, and (iii) new ideas are arising that change our understanding of disease mechanisms and/or the mechanism of action of a given drug. Finally, a major metric for the success of the ITN will be to make data and samples accessible to the community at large to expand opportunities for discovery. Achieving these goals will ultimately determine the utility of organizations such as the ITN.

TACKLING THE ULTIMATE CHALLENGE

The ITN has overcome many of the challenges faced by integrated clinical research networks. Its most basic and critical achievements account for its major successes to date: engaging a diverse group of professionals across multiple disciplines, in academia, industry, and government; developing an infrastructure that balances innovation, consistency, and quality control; and maintaining an open, inclusive framework that invites community input. However, a number of challenges remain, including the need to (i) reduce protocol development times to compete with industry timelines, (ii) develop and engage a set of highly competent clinical sites with minimal requirements for retraining, and (iii) optimize the internal use and external dissemination of data and tissue samples. We believe that these challenges can be solved through dialogue and coordinated efforts that force us to rethink the fundamental assumptions of translational research among the various stakeholders. The question now is whether the fruits of the ITN's labor will ultimately translate into new treatments.

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