

***NIH Roadmap: Reengineering the Clinical Research Enterprise
Regional Translational Research Centers
Interim Report***

The charge to this NIH Roadmap Working Group was to consider the implementation of regional centers that would provide NIH-funded investigators with the resources needed for state-of-the-art, safe, and cost-effective translational research. For this effort, translational research is defined as studies at the interface of the bench and bedside. The information flow is bi-directional, requiring close interaction of clinical and bench scientists. In this form of research, clinician and bench scientists advance the diagnosis of diseases and use their knowledge of natural history and pathogenesis to investigate, in early phase clinical studies (I-IIA), the effects of novel interventions. Complementing these clinical studies are laboratory investigations of clinical specimens that contribute to a fuller understanding of the diseases, their etiology, pathophysiology, pathogenesis, diagnosis, and treatment.

Consultants to the Roadmap working groups perceived that the lack of selected resources impedes movement of novel laboratory findings into the clinical arena, including the first-in human studies of novel drugs and biologicals. Some communities of investigators, such as those supported by comprehensive cancer centers or industry, can access such resources. For this reason, two specific sets of translational research initiatives, and working groups to implement them, were created. The first group is considering how best to provide investigators access to *Core Resources* that could prepare and take small molecules and biologicals through full preclinical testing as a prelude to justifying their study under an IND. Once such reagents, or others developed in the private sector, are prepared there will need to be sufficient resources to facilitate their study in humans. The second working group – the *Regional Translational Research Centers (RTRCs) Working Group* – was created, in part, to ensure the smooth “handoff” of these new products, as well as to support translational research in general. This RTRC Working Group was assembled of representatives of 12 NIH Institutes and Centers (ICs). The Working Group has had a series of meetings, including several with outside advisors. This interim report is intended to summarize the deliberations to date and current recommendations for potential implementation.

Needs Survey.

Discussions among Working Group members, and interviews with investigators at multiple academic health centers, revealed that substantive resources for translational research are already being provided by NIH ICs in the form of individual grants, training and career awards, and mission-specific Centers such as the Diabetes Education and Research Centers (National Institute of Diabetes and Digestive and Kidney Diseases), Translational Conte Centers (National Institute of Mental Health), the Immune Tolerance Network (National Institute of Allergy and Infectious Diseases), and the Comprehensive Cancer Centers (National Cancer Institute). The National Center for Research Resources supports about 80 General Clinical Research Centers (GCRCs) at a total cost of about \$300M/year. Each GCRC serves the needs of investigators within its own institutions, including provision of inpatient and outpatient beds, research coordinators, statistical consultations, some training, some regulatory oversight of protocols, and

some core laboratory support such as biochemistry and immunoassays. It was the consensus among academic investigators that their needs commonly extend beyond the resources of GCRCs at their own institutions. Collaborations that could build on the full range of clinical research resources currently funded by the NIH were seen as a cost-effective stimulus to translational research that would expand the patient base for individual studies and secure economies of scale. Regional Translational Research Centers might optimize their economies of scale if they were, individually, able to use the infrastructure of two or more GCRCs that formed a consortium with one or more of these additional clinical research resources.

Services provided through Regional Translational Research Centers.

Two potential levels of service are foreseen. Most (16-24) RTRCs would provide a broad menu of clinical research services to multiple institutions within a geographical region defined by acceptable patient access. Examples of these services are listed below and subsequently described in detail:

- a. Support new pilot research projects (analogous to the NIH bench-to-bedside award program) employing the resources of the collaborating institutions that feature a bench and a clinical scientist as co-principal investigators.
- b. Support for patient (particularly minority patient) recruitment cores.
- c. Assist with implementation of FDA Good Clinical Practice Regulations and the ICH Good Clinical Practice Consolidated Guideline in the development of human study protocols, their consent forms and requisite Investigational New Drug (IND) applications.
- d. Data accrual, curation and warehousing together with biostatistical support that extends beyond statistical consultation.
- e. Provision of clinical informatics platforms and services, including protocol tracking and the development of case record forms
- f. Central IRBs for protocols conducted by multiple institutions served by the Center.
- g. Support for specialized clinical staff, such as nurses with chemotherapy expertise and/or translational research fellows who cross disciplinary and institutional lines.

Support for bench and clinical investigators in new pilot research projects (analogous to the NIH bench-to-bedside award program) employing the resources of the collaborating institutions.

New resources are generally required to determine whether the clinical potential of a promising laboratory finding can, in fact, be realized. Such funds must be available promptly and be accompanied by an organizational structure that allows full compliance with regulatory requirements. Central review of Translational Research projects through the NIH is likely to be

too slow to match investigators' needs while experience with a pilot project program at GCRCs has shown that institutional committees can provide the critical levels of review that are necessary. The consortium of Clinical Research Centers on which the RTRCs will draw will be large and diverse enough to review pilot projects speedily and with the requisite depth of expertise.

Support for patient (particularly minority patient) recruitment cores.

Subject recruitment is time-consuming and can be advanced by dedicated personnel who achieve cost savings compared with physicians and nurses. Specialized recruiters can have ethnic, cultural and/or language characteristics that allow them access to populations who are otherwise reluctant to participate in clinical trials.

Assistance with implementation of FDA Good Clinical Practice Regulations and the ICH Good Clinical Practice Consolidated Guideline in the development of human study protocols, consent forms, and requisite IND applications.

Investigators' needs for assistance in meeting regulatory requirements are consistently heard and two Roadmap activities (Harmonization and NECTAR) should provide the middleware and software that will go some way towards addressing them. Computer programs alone will not suffice and the Workgroup recommended that each RTRC maintain an office with support for at least a clinical trials organizer and a secretary to prepare and submit documents to regulatory agencies for and on behalf of the investigatory team.

Data accrual, curation, and warehousing together with biostatistical support that extends beyond statistical consultation.

Good clinical practice guidelines require data accuracy and retrieval, together with an audit trail. Maintaining data quality goes beyond the resources of most single investigators, particularly under circumstances where data will be accrued from multiple institutions. The bioinformatics and biostatistical support available through GCRCs is designed primarily to support protocol development but does not in general support the flexibility and speed of response that a RTRC will require.

Central IRBs for protocols conducted by multiple institutions served by the RTRC.

Efficient recruitment of subjects requires that the research facility they visit be familiar and convenient for access. For an RTRC to meet this goal, multiple institutions will likely have to participate. Under these circumstances it will be important for a single IRB to satisfy the requirements of all participating institutions. There are numerous examples of "common" IRBs that serve multiple institutions, ranging from the large commercial "Western IRB" to smaller cooperatives at academic institutions. Investigators could be materially assisted if the institutions that were part of an RTRC were able to create and operate a shared "common" IRB for the purposes of translational research.

Support for specialized clinical staff, such as nurses with chemotherapy expertise and/or translational research fellows who cross disciplinary and institutional lines.

Current training programs, including the new Roadmap Multidisciplinary K12s, have an institutional basis that may create boundaries and impede clinical research. The working group believes that patient-oriented researchers capable of participating substantively in multidisciplinary teams will be needed. Moving across institutional lines would be desirable. Additional services to be provided at “Expanded Regional Translational Centers” (ERTRCs):

In addition to the services described above, a subset of expanded RTRCs (four to eight) would be supplemented by robust core laboratory technologies that could be applied to specimens shipped from elsewhere in the country that would be too costly and inefficient to replicate more widely. These technologies are needed for state-of-the-art studies of disease pathogenesis and early phase clinical interventions. The following are some of the technologies that are being actively considered by the Working Group:

- a. Immunophenotyping/high speed sorting in >four colors. Separating out tumor cells from populations of blood leukocytes has made advances in leukemia diagnosis and treatment possible. High speed, multi-parameter, cell sorters are needed; at a capital cost of \$500,000 these resources are most efficient if shared.
- b. RT-PCR core for expression array analyses. Microarrays for gene expression studies have brought new classifications to common tumors such as chronic lymphatic leukemia – but the technique needs to be well standardized to obtain reliable results. Rigorous control of the RT-PCR step will contribute more to the quality control of the process and make studies across multiple centers comparable.
- c. Real-time PCR. Quantitative endpoints extend the usefulness of PCR but are best performed under rigorously controlled conditions in a core lab.
- d. Informatics and expert statistical support to adequately interpret the genetic and microarray results.
- e. Pharmacological assays (LC-MS, etc.)
- f. Genomic and SNP sequencing resources will be required through a high throughput genotyping facility.

Mechanism: The Working Group has not defined the optimal granting mechanisms as yet, or whether the same mechanisms would best serve both types of RTRCs.

Costs: Preliminary estimates are that the routine RTRCs will cost ~\$3M per year, while the technologically enhanced RTRCs might cost \$5M per year.

Interactions with other NIH Roadmap projects: This initiative has potential interactions with other Roadmap projects, especially the NECTAR for electronic support, the Core Resources program for translational research, and the Interdisciplinary and Clinical Reengineering training efforts. The RTRCs could interact with the GCRCs, the NIH Clinical Research Center, and other NIH-funded centers programs.

Phased implementation: The Working Group has concluded that this program should evolve further in three phases. First, later in FY2004, or very early FY2005, the Working Group will convene a meeting of leaders representing a range of academic health centers, other centers programs, the GCRCs, and other relevant stakeholders, to be named. The goal is to draft and review for public comment the vision for the two types of RTRCs. Based on this meeting, an RFA(s) will be issued in early FY2005 to fund up to 30 one to two year planning grants at \$100,000 each to allow institutions within geographic regions to define the precise scope and governance of the Centers. Third, in FY2006 and succeeding years, RFAs will be issued to fund groups of RTRCs regionally and nationally.

The NIH Clinical Research Center might participate in RTRCs activities provided that comparable operating efficiencies were provided.

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