

PARTNERSHIPS

Translational cancer research comes of age in Latin America

Investigators of the U.S.–Latin America Cancer Research Network*†

The U.S.–Latin America Cancer Research Network strives to expand translational research capabilities and forge new collaborations.

Ambitious efforts to characterize the genomics of cancer, made by initiatives such as the Cancer Genome Atlas and the Global Cancer Genomics Consortium, have highlighted the disease's complexity and exposed how far we are from understanding the intrinsic molecular mechanisms that govern cancer outcome and response to therapy (1). Many of these cost-intensive studies used cutting-edge genomic technologies and were performed in developed countries with the support of national and regional agencies. Since then, investigators have delved more deeply into the effects of race and ethnic origin, and their intrinsic human genetic variation, on cancer susceptibility, prognosis, and response to therapy. Thus, cancer's complexity has created a challenge that encouraged concerted international efforts to improve the capacity for excellence in translational medicine research in developing countries. This unmet need spurred the Center for Global Health of the U.S. National Cancer Institute (NCI) to create the U.S.–Latin America Cancer Research Network (LACRN) (table S1), with the aim of strengthening collaborative research efforts among the participating countries, advancing translational cancer research, and reducing the global cancer burden. Here, we describe the implementation of the network's first translational study on breast cancer genomics (Table 1).

MODEL FOR INTERNATIONAL COLLABORATION

The LACRN comprises a coalition of research institutions; hospitals (mostly public); basic, translational, and clinical science investigators; and government officials through bilateral collaborative agreements between the U.S. Department of Health and Human Services and the governments of Argentina, Brazil, Chile, Mexico, and Uruguay. LACRN's first priority was to establish

scientific, technical, and oversight standards for research studies carried out by network participants. These standards include clinical protocol in compliance with the International Conference on Harmonization/Good Clinical Practice guidelines; standard operating procedures (SOPs) for project components (such as the roles and responsibilities of study team members, biospecimen handling, biomarker and endpoint assays); a comprehensive study-monitoring plan; and a research site-monitoring plan, as well as collaborative internal scientific and operational committees offering expertise from

all participating countries. With guidance from NCI, subject matter experts were appointed to design, implement, monitor, and maintain the study protocol, standards, and infrastructure components, such as biorepositories, and formed committees for informatics and data management, epidemiology, biobanking, cancer surgery, clinical oncology, pathology, basic research, applied technologies, biostatistics, and patient navigation. Also formed was a steering committee composed of national coordinators representing each member country that was supported by a comprehensive study monitoring plan, a virtual data coordination and analysis team (vDCAT), and a data sharing and publications committee.

A key component of the LACRN strategy was capacity building for both the network and individual member countries. Supportive business and research frameworks and facilities were established, including a comprehensive manual of operations that was updated through discussions among members (2). Project-team training was carried

Table 1. Building and broadening collaborations. LACRN timeline for collaborative cancer research efforts.

Year	Milestones
2009	<ul style="list-style-type: none"> • LACRN formed by LOIs* • First planning meeting, Bethesda, MD, USA • MPBC study protocol and SOP developed at workshop, Santiago, Chile
2010	<ul style="list-style-type: none"> • Initiation of monthly committee calls via teleconference and webinars • Pathology workshop, Rio de Janeiro, Brazil • Biobanking and molecular biology workshops, Montevideo, Uruguay • Bioinformatics workshop, Bethesda, MD, USA • Second LACRN annual meeting, Rio de Janeiro, Brazil
2011	<ul style="list-style-type: none"> • Biobanks established across LACRN countries • Residual cancer burden training, MD Anderson Cancer Center, Houston, TX, USA • Release of manual of operations and database in three languages • Start of patient recruitment for MPBC • Study monitoring plan implemented • Third LACRN annual meeting, Guadalajara, Mexico
2012	<ul style="list-style-type: none"> • First interim data analysis • First meeting of vDCAT, Buenos Aires, Argentina • Second interim data analysis • Fourth LACRN annual meeting, Buenos Aires, Argentina
2013–2014	<ul style="list-style-type: none"> • Bioinformatics training, Rio de Janeiro, Brazil • Third interim data analysis • REBLAC/RINC** and LACRN pathology and biobanking workshop, Rio de Janeiro, Brazil • MPBC study closed to patient accrual, December 2013 • LACRN strategic planning meeting, Bethesda, MD, USA • Future studies meeting, Lima, Peru

*LOIs, letters of intent to collaborate; **REBLAC/RINC, Red de Biobancos de Latinoamérica y Caribe/Red de Institutos Nacionales de Cáncer.

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out during the 2009 and 2010 planning phases through on-site meetings, workshops, and regularly scheduled webinars.

During implementation of the first clinical study protocol—“Molecular profiling of breast cancer in Latin American women with stage II and III breast cancer receiving standard neoadjuvant chemotherapy” (the MPBC study)—the network faced and overcame a number of challenges. In this context, the commitment of Latin American institutions involved not only the support for patients’ medical treatment (including diagnostics, surgery, medicine provision, and follow-up examinations) but also the lodging and maintenance of biorepositories and platforms for genomics- and bioinformatics-based translational studies (Table 1).

GOVERNANCE

LACRN governance is a collaborative management structure centered around the steering committee that oversees the progress of all network studies. Data integrity is a high priority for the network, and as an additional level of governance, data analyses are performed by each country’s vDCAT, which includes experts in clinical monitoring, epidemiology, pathology, genomic research, bioinformatics, and biostatistics. vDCATs create biyearly analyses of study data for the steering committee to review so that it can assess study progress, data quality and integrity, and study compliance with applicable regulations. The U.S. vDCAT performs interim analyses for the network as a whole, whereas the vDCATs from each Latin American country analyze the data corresponding to that specific country.

The data sharing and publications committee advises the steering committee on publication strategies and makes recommendations on proposals for the use of LACRN data or biospecimens for research within the LACRN or external collaborations. One national coordinator manages this committee, which includes representatives from each country appointed by the steering committee (fig. S1).

SUSTAINABILITY

Because LACRN seeks sustainability beyond its initial collaboration with NCI, high-quality, well-annotated biospecimens have been preserved in biorepositories that have detailed, field-tested SOPs for the collection and processing of tissue and blood, training of site personnel, establishment or improvement of research facilities, adop-

tion of an informatics system for tracking and managing biospecimen inventory, and application of quality control (QC) measures for specimen collection, processing, labeling, and storage. Pathologists were trained both in the evaluation of pathological complete response to therapy and residual cancer burden, both primary end points of LACRN’s clinical study of breast cancer. Intracountry and external (College of American Pathologists) evaluations were performed for immunohistochemical and *in situ* hybridization data.

Epidemiologists from all countries developed a common questionnaire that includes ancestry, family, and personal history of cancers; reproductive history; socioeconomic parameters; and lifestyle factors that may have affected the patients’ breast cancers. Subtle cultural and language differences among countries were addressed leading up to the creation of the final questionnaire in English, Spanish, and Portuguese, and a manual was developed with instructions for harmonizing the administration of the questionnaire across countries.

Using the open source system OpenClinica, electronic case report forms were implemented to capture clinical, genomic, molecular, and epidemiological data as well as biospecimen and microarray QC data. The databases also provide a link to the specimen-tracking system, assure that the data are usable and harmonized across the three languages, and serve as a basis for creating other informatics tools to support review of study progress and data analysis.

Creation of genomics platforms and development of the corresponding SOPs, QC measures, and methods for processing and analyzing molecular data were incorporated into the LACRN research effort. An intercountry proficiency test was performed in order to ensure harmonization of microarray expression data, and similar protocols are currently being adopted for other state-of-the-art technologies needed for future studies. Challenges included the varying internet technology infrastructures, capabilities, and logistics of the network countries; compliance with regulations that ensure security and quality of data; the need for multilingual capabilities; and the variety of data to be captured—clinical, epidemiological, microarray and other assay results, biospecimen tracking, and QC. Biorepository data were linked to deidentified patient data via a unique patient ID. The database, institutional review board (IRB) records,

and regulatory documentation follow U.S. regulations and are in compliance with U.S. policies on data privacy and security. The applicable regulatory requirements for each of the participating countries were also followed. For example, policies on sample use in Argentina, Brazil, and Uruguay demanded that enrolled patients sign an informed consent specific for the MPBC study; future use of samples and data in ancillary studies shall require reconsenting patients; in Chile and Mexico, future use of samples and data relies on local IRBs’ decisions, with no need for reconsenting patients.

FIRST STUDY: BREAST CANCER

Early in 2009, representatives from NCI and the five LACRN-participating Latin American countries agreed on a collaborative breast cancer project, the MPBC. Why breast cancer? Because with the exception of Argentina and Uruguay, the incidence of the disease is lower in Latin America than in high-income countries such as the United States (3, 4), and these lower incidences might correlate with variations in gene expression. Molecular classifiers of breast cancer such as Prosigna/PAM50, Mammprint, and Oncotype DX were trained and validated with populations of mostly European descent, but health disparities correlated to ethnic origin have been well documented. African American women suffering from breast cancer tend to have more aggressive tumors (with worse outcomes) than do Caucasian women (5), and an overrepresentation of triple-negative breast tumors exists in indigenous African women (6). Studies of genetic polymorphisms identified new single-nucleotide polymorphisms associated with breast cancer risk in African women (7) and Latin American women in the United States (8). These findings raise concerns about the applicability of risk markers defined in European populations to women of other ethnicities (9). The relative contribution of lifestyle and genetic susceptibility to breast cancer in Latin women remains unclear (10) and should be controlled in studies designed to test correlations between molecular markers and epidemiological factors or clinical outcome.

LACRN launched the MPBC study in ~40 hospitals and research institutions across the five Latin American countries, with the primary objective of characterizing, in Latin American women, the distribution of known molecular profiles of invasive breast cancer. The ultimate goal is to decipher genomic clas-

sifiers suited for disease heterogeneity and probability of recurrence in Latin American patients to improve prognosis. This information will be correlated with self-referred ancestry, known cancer risk, prognostic factors, and sociodemographic characteristics. Patient outcomes—measured as 3- and 5-year overall survival, time to first failure, and disease-free survival—will be used to assess the reliability of the prognostic classifier. The second part of the study will investigate the potential association between transcriptomic profiling and response to a harmonized neoadjuvant treatment so as to obtain a molecular classifier that predicts response to neoadjuvant chemotherapy.

Researchers collected biospecimens from 1436 enrolled participants, and an average of 10 blood-derived specimens (including whole blood, serum, plasma, and buffy coats) were obtained from each patient before neoadjuvancy and at the time of surgery. Also collected were core tumor biopsies and surgical resections taken from malignant tumors, nonmalignant adjacent tissue, macroscopically involved lymph nodes, and remnant tumor after neoadjuvancy. A total of 15,161 blood specimens, 7536 core biopsies, and 35,022 surgical resections have been collected across 25 recruitment sites and stored in 11 biorepositories across the five Latin American countries.

In 2012, the network expanded to include Colombia, Peru, and Puerto Rico and incorporated additional training on best practices in regulatory and compliance requirements. In the immediate scope of LACRN are projects involving genetic ancestry and targeted sequencing of breast cancer susceptibility genes. Future studies will involve whole-exome sequencing and identification of circulating tumor cells and

cell-free DNA. LACRN now stands ready to initiate academic collaborations with established networks around the world.

SUPPLEMENTARY MATERIALS

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Table S1. Full list of members of U.S.–Latin American Cancer Research Network.

Fig. S1. LACRN governance

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Supplementary Materials for

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Table S1. Full list of members of U.S.–Latin American Cancer Research Network.

Fig. S1. LACRN governance.

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Fig. S1. LACRN governance. The steering committee is responsible for overseeing all U.S.–L.A. CRN studies, making decisions regarding implementation of clinical research studies, developing infrastructure for the network, monitoring the progress of studies, and ensuring the proper sharing of specimens and data generated by the U.S.–L.A. CRN and proper publication of the network’s data. The steering committee is supported by a data coordination and analysis team, comprised of experts in all study disciplines and a Data Sharing and Publications Committee, along with discipline-based operational committees comprised of expertise from all countries, with guidance from US-NCI, including Informatics & Data Management, Epidemiology, Biobanking, Pathology, Clinical and Surgical Oncology, Pathology, Basic Research & Applied Technologies, Biostatistics, and Patient Navigation. Abbreviations: U.S.–L.A. CRN, U.S.–Latin America Cancer Research Network.