Published OnlineFirst March 23, 2010; DOI: 10.1158/1055-9965.EPI-10-0066

CEBP Focus: Biomarkers and Biospecimens

Global Perspectives

Establishment and Operation of a Biorepository for Molecular Epidemiologic Studies in Costa Rica

Bernal Cortés[1], Mark Schiffman[2], Rolando Herrero[1], Allan Hildesheim[2], Silvia Jiménez[1], Katheryn Shea[3], Paula González[1], Carolina Porras[2], Greivin Fallas[1], and Ana Cecilia Rodríguez[1]

Abstract

Background: The Proyecto Epidemiológico Guanacaste (PEG) has conducted several large studies related to human papillomavirus (HPV) and cervical cancer in Guanacaste, Costa Rica in a long-standing collaboration with the U.S. National Cancer Institute. To improve molecular epidemiology efforts and save costs, we have gradually transferred technology to Costa Rica, culminating in state-of-the-art laboratories and a biorepository to support a phase III clinical trial investigating the efficacy of HPV 16/18 vaccine.

Objective: Here, we describe the rationale and lessons learned in transferring molecular epidemiologic and biorepository technology to a developing country.

Results: At the outset of the PEG in the early 1990s, we shipped all specimens to repositories and laboratories in the United States, which created multiple problems. Since then, by intensive personal interactions between experts from the United States and Costa Rica, we have successfully transferred liquid-based cytology, HPV DNA testing and serology, chlamydia and gonorrhea testing, PCR-safe tissue processing, and viable cryopreservation. To accommodate the vaccine trial, a state-of-the-art repository opened in mid-2004. Approximately 15,000 to 50,000 samples are housed in the repository on any given day, and >500,000 specimens have been shipped, many using a custom-made dry shipper that permits exporting >20,000 specimens at a time. Quality control of shipments received by the NCI biorepository has revealed an error rate of <0.2%. Recently, the PEG repository has incorporated other activities; for example, large-scale aliquotting and long-term, cost-efficient storage of frozen specimens returned from the United States. Using Internet-based specimen tracking software has proven to be efficient even across borders.

Conclusion: For long-standing collaborations, it makes sense to transfer the molecular epidemiology expertise toward the source of specimens. The successes of the PEG molecular epidemiology laboratories and biorepository prove that the physical and informatics infrastructures of a modern biorepository can be transferred to a resource-limited and weather-challenged region. Technology transfer is an important and feasible goal of international collaborations. *Cancer Epidemiol Biomarkers Prev; 19(4); 916–22. ©2010 AACR.*

Introduction

The Proyecto Epidemiológico Guanacaste (PEG) is a research group that investigates human papillomavirus (HPV) and cervical cancer in Guanacaste, Costa Rica in a long-standing collaboration with the U.S. National Cancer Institute (NCI). Guanacaste is a rural province of Costa Rica, located 200 km northwest of San José, the capital.

For more than 10 years, biospecimens collected as part of those research efforts were shipped monthly to one of the NCI's biorepositories in the United States for storage. Blood separation was done at local clinical laboratories before shipment (1, 2). Specimens were stored in −20°C freezers and shipped in dry ice to NCI's repository, using a private shipping company to deal with the changing regulations of major commercial airlines. Although these conditions resulted in good quality for most specimens, there were notable exceptions when shipments were exposed to very hot temperatures in transit, or were delayed in customs. Moreover, international regulations tend to change, and the use of dry ice and possibly flammable specimen buffers (e.g., methanol in liquid-based

Authors' Affiliations: [1]Proyecto Epidemiológico Guanacaste, INCIENSA Foundation, San José, Costa Rica; [2]Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, Department of Health and Human Services, Rockville, Maryland; and [3]SeraCare Life Science, Frederick, Maryland

Corresponding Author: Bernal Cortés, Proyecto Epidemiológico Guanacaste, Fundación INCIENSA, Torre La Sabana, 7mo piso, Sabana Norte, San José, Costa Rica. Phone: 506-2220-3039; Fax: 506-2291-0832. E-mail: bcortes@proyectoguanacaste.org

doi: 10.1158/1055-9965.EPI-10-0066

Published OnlineFirst March 23, 2010; DOI: 10.1158/1055-9965.EPI-10-0066

cytology) led to periodic crises. It was difficult to maintain a predictable, steady flow of specimens to laboratories in the United States.

Our model of collection in Guanacaste, with shipment for high-technology work in the United States, was not suitable for tests that required rapid turnaround (e.g., HPV testing for clinical management) or required samples at cryogenic temperatures (e.g., cytokines and viable lymphocytes; refs. 3, 4). When, in early 2000, we decided to conduct a large (>7,000 participants), long-term community-based phase III clinical trial in Guanacaste, we augmented our intensive technology transfer. PEG and NCI researchers decided to establish state-of-the-art molecular epidemiology laboratories and a biorepository in Guanacaste.

The rationale was the following: for every test of every biospecimen in an international molecular epidemiologic study, there is a trade-off on whether to rely on local or distant (for us, the United States) expertise. One extreme requires little transfer of knowledge: the collection procedures can be simplified as much as possible, with the choice or even the development of instruments, buffers, tubes, and procedures that minimize the risk of failure even when the local staff is nonexpert. An experienced international shipping company can be hired, at high cost, to get the reagents to the site and to retrieve the specimens. With dry ice repacking or dry shippers, the specimens will hopefully arrive intact to the repository in the United States, and then to the participating expert laboratories throughout the world. This model is sufficient for brief cross-sectional surveys, in collaboration with local clinicians who will not continue with the research.

However, when the collaborators are dedicated to a long-term effort, technology transfer is important. Higher starting costs lead to lower later costs. More importantly, the transfer has the potential to create new centers of excellence in the region. In the PEG repository, we wished to enhance local capacity and improve specimen quality while reducing total project cost over its lifetime. Here, we describe the lessons learned, with a focus on why and how we established a modern biorepository in Costa Rica.

PEG Main Studies

The PEG natural history study of HPV and cervical neoplasia took place from 1993 to 2000; and prospectively studied a 10,000-woman random sample of Guanacaste. We stored specimens from >30,000 study visits, which have subsequently yielded >1,000,000 biospecimen aliquots now housed at NCI repositories in the United States. The biospecimen effort has cost millions of dollars since the study began, and storage costs in the United States, priced on a per vial basis, remain very high (we are now consolidating and culling specimens). Four small studies were conducted in the subsequent few years while the Costa Rican Vaccine Trial (CVT) was being planned. The CVT started in mid-2004 and recruited ~7,500 young women who randomly received the HPV 16/18 or hepatitis A (as control) vaccines at 0, 1, and 6 months. After the vaccination visits, participants attended follow-up visits for 4 years. Again, the number of biospecimens collected have been very large; however, we are limiting aliquotting and storing specimens in liquid nitrogen when possible, with an eye to long-term cost savings.

The study design, procedures, and specimen collection have been described elsewhere (5). In brief, at each visit, blood and cervical specimens (exfoliated cells and secretions) were collected from participants as appropriate. At the last visit, additional oral, vulvar, and anal samples were collected. Table 1 describes the specific requirements for each specimen collected per clinic visit.

Planning and Set-up of PEG's Biorepository

For PEG, the decision to create a repository was made based on the quantity of specimens expected for the CVT, preanalytic specimen needs (i.e., temperature requirements in shipping and storage), experience during the natural history study (1, 2), and our need to handle large amount of vaccines. The choice between different possible repository designs was supported by one of NCI's contract biorepositories, SeraCare Life Sciences (SCLS). On-site visits in Guanacaste were critical. SCLS advised us on equipment selection, standard operating procedures, and training. Importantly, the advice was ongoing and direct. PEG's biorepository was set up to store samples, oversee specimen transportation from PEG clinics, and distribute specimens to and from laboratories within Costa Rica. Periodic shipments to SCLS were scheduled for long-term storage and distribution to testing laboratories. In addition, the PEG repository stored and supported handling of the CVT vaccines.

The Biological Specimen Inventory System, a web-based bioresource management software used by the SCLS, and most NCI repositories, was selected to track samples in the repository. Communication among Costa Rican staff and U.S. parties was facilitated by using a single database, without extra data management needed to track samples among borders or maintaining documentation of the specimens' history. Many local research groups have very limited experience in specimen management, from the correct choice of labels to use at different temperatures to the fundamentals of how to box and rack biospecimens most efficiently in low-temperature freezers. Finding staff with excellent prior understanding of the dynamics of repository databases can be difficult, but direct, continued training of highly motivated individuals, some with a background in quality control for manufacturing (not health research), was the key to success.

The answer proved to be the adoption of NCI-SCLS protocols, rather than trying to "reinvent the wheel." Standard operating procedures were developed adapting those of SCLS to standardize all major aspects as

Published OnlineFirst March 23, 2010; DOI: 10.1158/1055-9965.EPI-10-0066

Table 1. Summary of the original specimens handled by the repository, the temperatures at which specimens were maintained prior to processing or reception at the repository, samples obtained after processing, storage temperature of the final specimens, and the expected use of the specimens

Original material	Transport temperature	Sample obtained	Storage temperature	Expected use of the specimen within the CVT
Clotted blood (8 mL)	4°C	Serum	LN_2 vapor phase	Nutrients, DNA, immunologic and hormonal assay
Peripheral blood, ACD preserved (8 mL)	4°C	Buffy coat, RBC, whole blood, ascorbic acid added plasma, plasma	LN_2 vapor phase	Nutrients, DNA, immunologic and hormonal assay
Peripheral blood, EDTA preserved (4 mL)	4°C	Plasma	LN_2 vapor phase	Nutrients, immunologic and hormonal assay
Scope mouthwash	4°C	Oral cells	LN_2 vapor phase	Oral HPV DNA
Heparin-preserved blood (32 mL)	20°C	Peripheral blood mononuclear cells, plasma	LN_2 vapor phase	Cytokines and local immunity assays
Biopsy or LEEP	20°C	Histology slides and histologic blocks	Room temperature	Diagnostic, treatment, genetic and immunologic assays
Cervical cells preserved in PreservCyt solution	20°C	Cytology slide, residual PreservCyt; 0.5 mL cervical cells aliquot	Room temperature LN_2 vapor phase	HPV DNA, cervical cytologic and infection diagnosis; chlamydia and gonorrhea DNA tests
Self-collected cervical cells	LN_2 vapor phase	No processing needed prior to storage	LN_2 vapor phase	HPV DNA
Clinician-collected cervical cells	LN_2 vapor phase	No processing needed prior to storage	LN_2 vapor phase	HPV DNA/RNA
Cervical secretions	LN_2 vapor phase	No processing needed prior to storage	LN_2 vapor phase	Cytokines and local immunity assays
Vulvar cells	LN_2 vapor phase	No processing needed prior to storage	LN_2 vapor phase	HPV DNA
Anal cells	LN_2 vapor phase	No processing needed prior to storage	LN_2 vapor phase	HPV DNA

Abbreviations: ACD, acid citrate dextrose; LEEP, loop electrosurgical excision procedure; LN_2, liquid nitrogen.

suggested by the International Society for Biological and Environmental Repositories Best Practices (6). For example, in the PEG repository, participants' clinical data and specimen data (i.e., participant-visit-sample link, problems during collection or processing, collection to processing time) are handled in a separate database, which assures confidentiality (5). Bidimensional bar-coded labels are used to uniquely identify each sample, reduce keying errors, improve quality control and increase processing speed.

Initial Set-up and Operation Cost

Initial set-up cost is high, in particular, for material and equipment when acquired in Costa Rica (e.g., a large-capacity liquid nitrogen freezer costs around $31,000 in the United States versus $37,000 in Costa Rica) and the necessity to bring experts to Costa Rica for the different components of training. On the other hand, facility rentals may be found around $1.00 to $3.00 per square meter, electricity cost is around $6.30 per 1,000 kw/h. Salaries are one of the biggest costs in any organization. Salaries in Costa Rica are, in general, lower than those in the United States, although in our studies, one of the key aspects has always been to remunerate our workers with better than the usual local wages. As a reference, in Costa Rica, the minimum salary for a biologist with a bachelor degree is around $600 a month plus fringe benefits. Therefore, once staff members are well-trained, they can be paid excellent local salaries to maintain their participation, but with much lower costs than a U.S. based effort. This can be viewed from the NCI side as preemptive outsourcing of study activities to reduce costs.

Specimen Transportation

Specimens collected by the PEG repository requiring immediate freezing are collected in liquid nitrogen in clinics, and transported in liquid nitrogen dry shippers

Published OnlineFirst March 23, 2010; DOI: 10.1158/1055-9965.EPI-10-0066

(e.g., cervical secretions used to test for cytokines, cervical cells for HPV testing for which we want to maintain a good chance of finding RNA). Other specimens are transported in coolers at the required temperature for up to 24 hours (e.g., blood). Dry shippers and coolers were selected instead of electrical freezers for short-term storage and transport because they don't need electricity and are equipped with dual alarm thermometers. Training specific for each standard operating procedure is mandatory for all personnel involved in the collection, transportation, and processing of specimens (5, 7).

Specimen Processing

After the intense CVT vaccination phase ended (2006), specimen and vaccine handling declined; in their place, the repository staff took on laboratory activities. Rather than using clinical laboratories, they started separating and preparing blood aliquots for the planned blood tests (as noted above, the optimal number of aliquots should now take into account expensive long-term storage requirements). The cytology staining laboratory; which had been created separately, was incorporated to the repository in 2008. We created a liquid-based cytology effort because it was taking many months to transport slides and receive diagnoses from the United States, which was hampering the clinical protocols. A similar decision led to the creation of HPV testing, and CT/CG testing laboratory efforts. These laboratories match standards in the United States, due to years of interactive Quality Assurance (QA) work. Finally, the cryopreservation laboratory that we had established in San José was moved to the repository, to reduce collection to processing time from 24 hours to less than 12 hours, essential for the viability of cryopreserved lymphocytes. Over 30,000 specimens have been processed and more than 65,000 derived samples have been produced by

Table 2. Specimens collected, processed, and exported by the PEG repository from July 2004 to December 2009

Specimen type (additive/ collection-transport medium)	Samples produced in the repository (%)*	Exported by December 2009	Stored at repository by December 2009	Total
Buffy coat	4,630 (43)	9,954	790	10,744
Cervical cells (in PreservCyt solution)	6,477 (20)	28,129	3,976	32,105
Cervical cell aliquots,† 0.5 mL (from PreservCyt vials)	6,477 (21)	28,330	2,012	30,342
Cervical cell aliquots, 0.5 mL (from PreservCyt vial)	6,477 (22)	27,488	1,568	29,056
Cervical cells (UCM transport medium)	No processing needed	27,610	731	28,341
Cervical secretions	No processing needed	36,429	1,444	37,873
Peripheral blood mononuclear cells (Heparin)	4,763 (8)	58,003	76	58,079
Plasma (10% metaphosphoric acid added)	4,630 (43)	9,954	790	10,744
Plasma (ACD, yellow tube)	18,448 (43)	39,711	3,156	42,867
Plasma (EDTA)	8,294 (100)	7,276	1,018	8,294
Plasma (heparin)	6,330 (8)	76,229	1,037	77,266
RBC (ACD, yellow tube)	4,630 (43)	9,965	790	10,755
Serum (zinc-free, serum separation tube)	29,485 (23)	126,585	2,861	129,446
Thinprep slide	6,223 (19)	31,496	1,046	32,542
Biopsy block (paraffin-embedded cervical biopsy)	348 (23)	1,226	302	1,528
Biopsy slide (H&E stained, biopsy slide)	361 (23)	1,531	50	1,581
LEEP block (paraffin-embedded cervical LEEP)	450 (15)	2,591	407	2,998
LEEP slide (H&E stained, LEEP slide)	467 (15)	3,009	46	3,055
Self-collected cervical cells (PreservCyt solution)	5,225 (100)	5,225	0	5,225
Anal cells (PreservCyt solution)†	No processing needed	300	2,091	2,391
Vulvar cells (PreservCyt solution)†	No processing needed	300	2,843	3,143
Oral cells (mouth wash)†	No processing needed	300	3,181	3,481
Whole blood (3% ascorbic acid added)	4,665 (43)	8,450	2,559	11,009
Total	123,886	540,091	32,774	572,865

NOTE: The PEG repository houses approximately 54,000 specimens at any given day, which represents over 550,000 daughter samples.

*Values between parentheses represents the percentage of all samples ever banked at the repository that has been produced at the repository.

†Specimens exported to DDL.

Published OnlineFirst March 23, 2010; DOI: 10.1158/1055-9965.EPI-10-0066

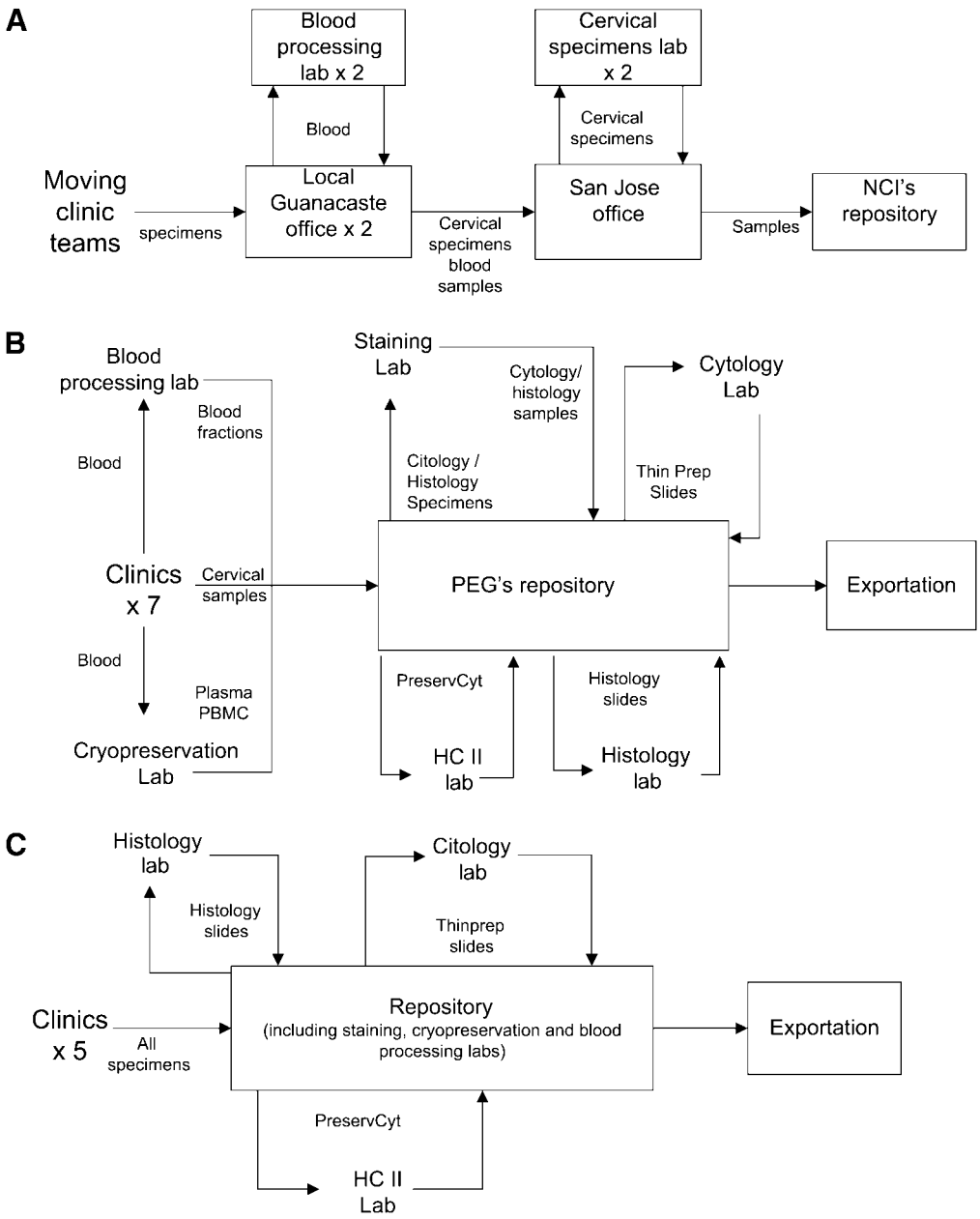

Figure 1. A, handling of specimens prior to PEG repository set-up. All specimens were sent to two local offices, blood specimens were sent to external laboratories for same-day processing, all samples were sent to PEG headquarters in San José on a weekly basis. Diagnostic cervical specimens were sent weekly to San José headquarters, and from there, to external laboratories for processing and diagnosis. All samples were sent to NCI's repository for storage and further laboratory distribution on a monthly basis. B, the handling of specimens once PEG repository started operations but before the start of processing activities by the repository at the time blood specimens were sent to external laboratories for processing. PreservCyt vials were received at the repository and sent to an outside laboratory for production and staining of the Pap smear slide. After returning to the repository, the PreservCyt vials were sent to an outside PEG laboratory for HPV testing and then returned to the repository. C, specimen handling after the repository incorporated specimen-processing activities.

the repository (see Table 2 for details). The life cycle of specimens within Costa Rica is summarized in Fig. 1. For each new technique introduced, an expert interacted directly and extensively with staff on-site to assure quality of performance.

Specimen Storage and Exportation

Specimens banked at the repository are maintained at two different temperature ranges: non–temperature-sensitive samples are maintained at controlled room

Published OnlineFirst March 23, 2010; DOI: 10.1158/1055-9965.EPI-10-0066

temperature (23°C to 27°C), whereas the rest are stored in large-capacity liquid nitrogen vapor freezers at a range of −150°C to −190°C. Liquid nitrogen freezers were chosen due to frequent power outages, suitability of cryogenic temperature during storage, and local and international transport and exportation. Approximately 17,000 to 50,000 samples are now housed in the repository on any given day and >100,000 specimens have been shipped to and returned from different local laboratories. For exportation of large amounts of frozen vials, the repository has custom-made large dry shippers that can hold up to 25,000 specimens (2 mL cryovials), over 50 times the capacity of regular field dry shippers. This permits us to reduce shipment frequency and cost per sample shipped ($0.17 per vial assuming 25,000 2-mL cryovials using the large shipper against $1.00 assuming field shipper). We also are able to nearly eliminate resources consumed by shipment preparation.

Through this approach, with minimal handling of specimens once entered into the repository, <50 samples have been found on audit to be in an incorrect location (<0.2%). Besides this check, >15,000 samples have been retrieved from SCLS for processing and/or testing. Over 500,000 samples have been exported to SCLS and over 25,000 specimens have been exported to the Netherlands for HPV testing (4), with very high quality (see Table 2).

State-of-the-art repositories require firm adherence to multiple standard procedures. The repository incorporated common industrial best practices applicable to our organization (NCI Best Practice, International Society for Biological and Environmental Repositories Best Practices, Current Good Laboratory and Clinical Practices); for example, 24-hour surveillance with emergency response teams, constant training, quality assurance system, compliance with applicable regulations, occupational safety measures, power back-up system, implementation of an inventory control system, and others.

Lessons Learned

During the course of the study, the repository has faced multiple difficulties and although most of them were overcome, it still faces frequent challenges. The constant availability of consulting experts who are dedicated to the effort and respond to biorepository staff questions has been a key factor for the biorepository success. The facility used for the repository was originally built for other purposes and therefore was not ideal and required building modifications, PEG headquarters were recently moved to a new facility that allowed improved overall repository and laboratory conditions. Slow Internet when using the distributed biospecimen inventory system was an issue during the start of repository operation but that was solved as the province's telecommunications improved. Although liquid nitrogen supply was available in the country, we have faced multiple problems including high cost (from around $0.50 to $0.95 per liter, depending on multiple local factors) and availability of required low pressure containers from the vendor. Currently, the liquid nitrogen supply runs smoothly.

Importing reagents including the vaccines and exporting large numbers of biological specimens was a complex process due to a lack of experience not only from our side but from local custom agencies as well. Mock shipments were done prior to the first real shipment. We have learned to discuss yearly versions of the International Air Transport Association (IATA) guidelines in advance with custom agents and SCLS staff to prevent shipping delays or problems, which are now unusual.

Obtaining specialized maintenance services is still time-consuming and expensive because experts have to travel from San José or from other countries; also, many spare parts have to be imported. Maintenance and repair contracts were established with different equipment representatives, allowing for proper spare parts stocked at the repository, training on basic maintenance, remote assistance, and quality control programs. Assuring the provision of laboratory reagents and supplies requires ordering with careful anticipation and storing of extra provisions.

Future of the Biorepository

The PEG repository has recently launched a multicenter pilot phase III clinical trial for the eradication of *Helicobacter pylori*, which will enroll and follow 210 participants for 1 year. In addition, an observational study is starting to provide a 6-year follow-up of women who were vaccinated against HPV 16/18 in CVT (n = 3,500) and a group of women who have not received vaccination against HPV ($n \sim 3{,}000$). Another observational study will provide a final screening at 20 years post-enrollment for selected women from a 10,000-woman natural history cohort.

In addition, the repository has recently received a new vaccine shipment for the cross-over vaccination study which will involve participants from the CVT. In a very interesting development, the repository is now receiving more than 30,000 specimens from previous epidemiologic PEG studies, which are currently stored at SCLS, for cost-efficient long-term storage. They are returned in what would otherwise be empty large dry shippers. The low operating costs of the PEG repository make it a valuable part of the large NCI repository resource.

Conclusion

As the result of years of vigorous technology transfer, with many direct contacts between established experts and Costa Rican staff, we have found that integrating the handling and processing of specimens within PEG headquarters was not only feasible but that it reduced specimen handling (see Fig. 1) and study costs. The success of PEG's biorepository in a rural province of Costa Rica within a resource-limited and climate-challenged region proves that the physical,

Published OnlineFirst March 23, 2010; DOI: 10.1158/1055-9965.EPI-10-0066

organizational, and informatics infrastructure of a modern biorepository can be effectively transferred to such a region. The PEG repository is now formally acknowledged as an NCI repository, with reverse traffic of valuable specimens to it for cost-efficient storage. We consider that the establishment of this repository has improved the quality of the scientific information produced in our studies, allowing, at the same time, multiple opportunities for additional collaborations with local and international scientists. Potential scientific trade-offs include difficulties encountered in the initial phases that could reduce the quality of the specimens and therefore of the data during the learning process. However, with proper training and supervision, this problem can be kept to a minimum, leading to long-term gains and the establishment of a regional center of scientific excellence.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Grant Support

The population-based natural history study of HPV infection and cervical neoplasia in Guanacaste, Costa Rica was supported by the NIH (N01-CP-21081, N01-CP-33061, N01-CP-40542, N01-CP-50535, N01-CP-81023). The HPV Vaccine trial is sponsored and funded by NCI (N01-CP-11005) with support from the NIH Office for Research on Women's Health.

Received 01/15/2010; revised 02/12/2010; accepted 02/23/2010; published OnlineFirst 03/23/2010.

References

1. Herrero R, Schiffman M, Bratti C, et al. Design and methods of a population-based natural history study of cervical neoplasia in a rural province of Costa Rica: the Guanacaste project. Rev Panam Salud Publica 1997;1:362–75.
2. Bratti M, Rodriguez A, Schiffman M, et al. Description of a seven-year prospective study of human papillomavirus infection and cervical neoplasia among 10000 women in Guanacaste, Costa Rica. Rev Panam Salud Publica 2004;15:75–89.
3. Holland N, Smith M, Eskenazi B, Bastaki M. Biological sample collection and processing for molecular epidemiological studies. Mutat Res 2003;543:217–34.
4. Fowke K, Behnke J, Hanson C, Shea K, Consentino M. Apoptosis: a method for evaluating the cryopreservation of whole blood and peripheral blood mononuclear cells. J Immunol Methods 2000;244:139–44.
5. Herrero R, Hildesheim A, Rodriguez A, et al. Rationale and design of a community-based double-blind randomized clinical trial of an HPV 16 and 18 vaccine in Guanacaste, Costa Rica. Vaccine 2008;26:4795–808.
6. International Society for Biological and Environmental Repositories. Best practices for repositories collection, storage, retrieval and distribution of biological material for research. Cell Preserv Technol 2008;6:1–8.
7. Porras C, Safaeian M, Gonzalez P, et al. Epidemiology of genital *Chlamydia trachomatis* infection among young women in Costa Rica. Sex Transm Dis 2008;35:461–8.

Cancer Epidemiology, Biomarkers & Prevention

AACR American Association for Cancer Research

Establishment and Operation of a Biorepository for Molecular Epidemiologic Studies in Costa Rica

Bernal Cortés, Mark Schiffman, Rolando Herrero, et al.

Cancer Epidemiol Biomarkers Prev 2010;19:916-922. Published OnlineFirst March 23, 2010.