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### Human Papillomavirus - July 2008

Interview Date: October 2008



#### Dr. Rolando Herrero

From the Special Topic of [Human Papillomavirus](#)

*According to our Special Topics analysis of HPV research over the past decade, the work of Dr. Rolando Herrero ranks at #6 by both total cites and by number of papers, with 59 papers cited a total of 3,191 times. Four of these papers are included in the top 20 papers lists in this Topic. In [Essential Science Indicators<sup>SM</sup>](#) from [Thomson Reuters](#), Dr. Herrero's work includes 188 papers, the majority of which are classified in the field of Clinical Medicine, cited a total of 5,346 times between January 1, 1998 and June 30, 2008.*

*Dr. Herrero is a researcher at the Fundación INCIENSA in San Jose, Costa Rica. In the interview below, ScienceWatch.com correspondent Gary Taubes talks with him about his highly cited HPV research.*

#### SW: What factors or circumstances led you to your research on HPV and cervical cancer?

Well, when I started my career 25 years ago, we had—and we still have—an enormous problem with cervical cancer in Costa Rica. It was clear to me back then that treating cancer that had already developed was not sufficient—we needed to develop new forms of prevention. I am a medical oncologist, and as I was finishing my training in the mid-1980s, there was a large case-control study of cervical cancer starting up, in collaboration with the US National Cancer Institute (NCI), which included markers for HPV, and one of the sites was in Costa Rica. I was fascinated by the techniques, by the epidemiology and particularly epidemiology done with resources—high-tech epidemiology. I had never seen that before, because it basically didn't exist here in Costa Rica. And this research spoke directly to the origins of disease. It was very, very exciting, and I started collaborating. I liked it so much that I kept it up.

Eventually I became the principal investigator for Costa Rica in that study. The coordinators—Louise Brinton and William Reeves—suggested I come to the US and do some analysis of the data at the NCI. I stayed for three years and planned the next series of studies while I was there. When I came back, I conducted those studies.

#### SW: Was your highly cited 2003 *New England Journal of Medicine* paper (Muñoz N, et al., "Epidemiologic classification of human papillomavirus types associated with cervical cancer," *NEJM* 348[6]: 518-27, 6 February 2003) an NCI collaboration?

No, not at all. In 1995, I moved to France to work at the World Health Organization's International Agency for Research on Cancer, IARC, and there we coordinated a large

program, a series of case-control studies, pretty much along the lines of what I had already done in Costa Rica. But this was a multi-national, multi-center study. We did multiple studies of cervical cancer, and a large multi-center case-control study of oral cancer and HPV. We also did some population-based surveys to assess the prevalence of HPVs in different areas. I had the opportunity to coordinate, organize, conduct, and analyze these studies.

Eventually we merged a whole series of the cervical cancer studies into a pooled analysis of HPV prevalence in these tumors. That was the *New England Journal of Medicine* paper with Nubia Muñoz as the first author. We were looking at all the different types of HPV detected in cervical cancers. There are about 40 HPV types, and we were able to rank them based on what fraction of cancers worldwide could be attributed to each type: HPV-16 is responsible for 50% of cervical cancer, HPV-18 for 20%, etc.

**SW: What are the challenges to doing this kind of epidemiological research in Costa Rica that you might not have elsewhere?**

Well, there are many challenges to this work in general, particularly when the studies include new screening methods for vaccines. We have to coordinate many different groups, because we have the field effort on one hand; we have the collaborators in the States, the companies, the FDA, all the independent regulatory boards, and all the committees that supervise this work on the other. We have laboratories in different areas of the world that are doing different kinds of assays, all related to the same projects. This type of coordination is the most challenging.

Then, in Costa Rica, these studies are conducted mainly in rural areas and that creates logistical and transportation problems. Sometimes it's challenging in terms of administration of resources, supervision of studies. You have to make sure there is appropriate medical supervision. You have to find the right groups to supervise, make sure you comply with all the international regulations, which can be stricter than they are internally. You have to be very active in public relations. You have to explain to the public what it is you're doing. And you have to get the support of your own government, and when you're collaborating with other governments, you have to make sure there's fluid interaction between them. So all of that can be challenging.

But I would say we also have an enormous advantage here. We have a universal healthcare system. People are used to being part of it; they trust the health system and they show a lot of interest in participating in these kinds of studies.

**SW: What professional accomplishments give you the most satisfaction?**

What I'm most proud of is that we now have developed a very large team here; we have team of more than 100 people that is fully dedicated to research on cervical cancer. We have trained scientists, epidemiologists, physicians, microbiologists, molecular biologists, and statisticians. The Guanacaste Project is a large research center, fully dedicated to HPV and cervical cancer. It is a tremendous tool. We are constantly developing new protocols, new projects, and implementing them in the field. We have clinics, laboratories, and repositories with computer systems, and different kinds of populations to study. That is all very rewarding, that we've managed to set up such a large and efficient group. And they are dedicated. I think it's unique in terms of how specialized they are, how focused they are on one condition, which is such a big problem in Latin America and in developing countries throughout the world.

**SW: What is the current focus of your research?**

We're now doing a large clinical trial of an HPV vaccine against type 16 and 18—the GlaxoSmithKline vaccine. This is being done with funding from the NCI and the support of several institutions here. It is an independent trial, by which I mean it's not sponsored by the company or run by the company. It is run by the investigators and that gives it a unique quality. Most drug trials are done and administered, analyzed and published by the companies themselves. In this case, GSK gave us the vaccine, but we're doing the work; we're doing the analysis and writing up the publications together with our colleagues at the NCI. It's good for everybody and for the company, which would like to see their results confirmed by independent investigators.

We're focusing on the efficacy of the vaccine, but we're also looking at the mechanism of protection of the vaccine, in relation to the immune response, humoral, and cell-mediated. We're very involved in

*"If the vaccine can reach a price that's affordable, it can definitely play a significant role, particularly in areas where screening programs are very hard to establish."*

looking at all these immunological mechanisms, including the genetics of the immunologic response: what cell groups are activated in response to the vaccine, and also in response to natural infection.

"...there are many challenges to this work in general..."

We're also interested in the impact of the vaccine on the population: what happens in certain subgroups when they're vaccinated, such as different age groups. What happens when you vaccinate women who were previously exposed to the virus? We had a paper that we published in *JAMA* last year, in which we analyzed the efficacy of the vaccine to induce regression of infections that were already present (Hildesheim A, *et al.*, "Effect of human papillomavirus 16/18 L1 viruslike particle vaccine among young women with preexisting infection - A randomized trial," *JAMA* 298[7]: 743-53, 15 August 2007).

#### **SW: What did you find?**

We found no impact at all on the regression of lesions. There is no therapeutic efficacy, only prophylactic.

#### **SW: How do you see HPV vaccines playing a role in Costa Rica?**

The problem is that the vaccine is extremely expensive. It's currently out of reach of developing countries, which is where it's mostly needed. Eighty percent of cervical cancer cases occur in developing countries. If the vaccine can reach a price that's affordable, it can definitely play a significant role, particularly in areas where screening programs are very hard to establish. In those areas, if the vaccine is affordable, it can have significant impact. In a way, it's much simpler to give a vaccine than it is to set up a lifetime program that requires multiple contacts over the course of your life.

#### **SW: What would you like to convey to the general public about your work?**

Well, from a public health perspective, that it's important to realize that cervical cancer is a very serious problem. We now have several very novel ways to prevent it, to control it, and this information has to be disseminated. We have to make sure that governments do all that they can to put these programs in place and achieve protection against this disease.

It's still completely out of control in most developing countries, while it's almost controlled in developed countries. It's one of the most severe examples of inequality, both between countries as well as within countries. It's also the poorest women in developed countries that get this disease, mainly because of a lack of access to the right health services. I'd also say that it's very useful to do this kind of research and very rewarding to collaborate, in terms of the technology transfer between Costa Rica and the NCI. Not only is there direct benefit to the public health in Costa Rica, but this problem is common worldwide and what we learn here can be applied directly to other countries and contribute to medical knowledge everywhere. ■

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#### **Dr. Rolando Herrero's current most-cited paper in *Essential Science Indicators*, with 856 cites:**

Muñoz N, *et al.*, "Epidemiologic classification of human papillomavirus types associated with cervical cancer," *N. Engl. J. Med.* 348(6): 518-27, 6 February 2003. Source: *Essential Science Indicators* from Thomson Reuters.

Keywords: HPV, papilloma virus types, vaccine, cervical cancer, vaccine cost, population-based screening, epidemiology, case-control studies, Costa Rica.



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