



# Collaboration in the War against Viruses: A Multidisciplinary International Effort

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As I write this article, we are experiencing two epidemics: a global epidemic of disease (COVID-19) caused by a novel coronavirus (SARS-CoV-2), and an epidemic of panic caused by the uncertainty about the disease and its consequences. A solution to both of these epidemics is, of course, knowledge derived through research. Globally, efforts are now focused on understanding the natural history of the COVID-19 infection and on development of interventions, including vaccines to prevent infection and treatments for the disease. In addition, we need research on how to better convey information to the general public to avoid over-reaction and panic in the face of uncertainty. Research on coronaviruses, like any other research, is most effective if it is adequately funded and researchers have the necessary skill sets. For COVID-19, we need research expertise in both basic and applied sciences, including not only health sciences but also technological sciences, social sciences, biology, chemistry, and epidemiology, to maximize the impact and benefit of this targeted research to the community.

Preparedness for epidemics should not wait till an epidemic arrives! In my lifetime, I have experienced epidemic diseases caused by newly recognized viruses, including hepatitis C, HIV/AIDS, SARS-CoV-1, MERS, Lassa fever, Zika virus, and Ebolavirus, as well as Yellow Fever, influenza, and measles virus, which are more common but equally severe. For all these epidemics, we need to be prepared and have teams of researchers ready to handle the unexpected! One aspect of preparedness pertinent to this journal is that the efforts in research will be most effective if undertaken through collaborations—between global researchers, between health care professionals researchers and governments, and between researchers and the general public—to ensure that research produces outcomes of real benefit to the community, who are the true end users of our research.

My lifetime research focus has been cervical cancer, a disease of global epidemic proportions, killing over 300,000 women worldwide each year. The disease is caused entirely by infection with human papillomaviruses (HPV). These infections are of equally epidemic nature, as more than half of all the adult population are infected with cancer-causing HPVs at some time in their lives. Fortunately, most infected people clear the infection themselves, through largely unknown mechanisms.

Research to understand cervical cancer began with an Italian mathematician and epidemiologist Dr Rigoni-Stern in the mid-nineteenth century.<sup>1</sup> His work

DOI:[https://doi.org/10.1016/](https://doi.org/10.1016/j.xinn.2020.04.011)

[j.xinn.2020.04.011](https://doi.org/10.1016/j.xinn.2020.04.011)

<http://www.cell.com/the-innovation>

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demonstrated that cervical cancer was significantly more common in married women than nuns, an observation that remained unexplained for over 100 years, although knowledge of how to control this disease was developed meanwhile through the work of US-based Greek pathologist, George Papanicolaou, in the 1920s. He demonstrated that cancer and pre-cancer cells could be found in the neck of the womb in women before they developed disseminated disease, thus leading to an effective way of controlling cervical cancer through early treatment.<sup>2</sup> However, it took 20 years before other researchers adopted and accepted this approach, and around 50 years before routine screening for cervical cancer started to have an impact on the global prevalence of this common disease.<sup>3</sup> In the meantime, the link between sexual activity and cervical cancer was reconfirmed epidemiologically, and serological association of cervical cancer with one possible infection, herpes virus, was given as a possible explanation of the link.<sup>4</sup> However, German virologist, Harald zur Hausen, and his knowledge of oncogenic animal viruses, enabled him to develop a hypothesis in the late 1970s that the causal virus of cervical cancer might be a papillomavirus,<sup>5</sup> because HPVs were transmitted through sexual activity, and animal papillomaviruses were known to be associated with cancers in cattle, rabbits, and dogs. His team, building on newly available technology, was able to demonstrate genetic signatures of HPV in some cervical cancer samples.<sup>6</sup> This observation initiated a global effort by many research groups<sup>7,8</sup> that confirmed that one family of HPVs, the  $\alpha$ -HPVs, includes specific genotypes whose genes could immortalize cell lines in the lab. These findings completed a loop of evidence that the observed association of high-risk HPVs with cervical cancer was likely causal. Not only cervical cancer, but also cancers at other anogenital sites and some oropharyngeal cancers, are now recognized to be associated with persistent HPV infection.

Discovery by zur Hausen and his colleagues of a virus causally connected to cervical cancer laid the founda-

tion for the development of HPV vaccines to prevent this disease, especially once it was established that HPV infection was common, and progression to cancer slow and not particularly common. The then conventional approaches to the development of a new vaccine were precluded because HPV could not be grown in the lab, which would be necessary to enable development of an attenuated virus vaccine or a killed virus vaccine. However, technological developments enabled progress on HPV vaccines. The then newly achieved ability to express genes in cell culture enabled laboratory production of HPV proteins. Prokaryotic expression systems were initially used to produce virus-encoded proteins, but the proteins produced lacked the three-dimensional conformation of the proteins as assembled in the native virus, and the antibodies they induced in animals were ineffective at binding and neutralizing HPV. When eukaryotic expression systems were developed, my Chinese colleague in virology, Dr. Jian Zhou, whom I met while on sabbatical in Cambridge, England, agreed with me to try to assemble the HPV shell when he came to work in my lab in Brisbane, Australia, in 1990. Eukaryotic cell expression of virus genes cloned from a clinical specimen into a vaccinia expression vector, with gene translation initiated from an appropriate start codon, turned out to be successful in producing assembled capsid proteins in monkey kidney cells,<sup>9</sup> whereas virus genes cloned from a cancer had sequence errors that precluded efficient capsid assembly even in a eukaryotic expression system.<sup>10</sup> Over the next few years, we and other researchers used more efficient gene expression systems (baculovirus, yeast)<sup>11-13</sup> to produce larger quantities of correctly conformed viral capsid proteins, and these, when used as the basis of a vaccine, induced an antibody that bound to the HPV capsid. These vaccines were shown to prevent papilloma virus infection in animal models, and then to prevent papilloma virus infection and cervical precancer in humans, first in commercially funded clinical trials, and subsequently in epidemiological studies in countries where vaccination had been routinely introduced.<sup>14</sup>



**Figure 1** Multidisciplinary International Collaboration

There are take-home messages from the story of the HPV vaccine for future research on epidemic prevention. These include the importance of

- 1) development of new enabling technologies that drive research progress; investment in development of new technologies is critical for moving research forward, even if there is no immediate application envisaged for the technology
- 2) collaboration across research disciplines to enable discoveries that would be less likely without such collaborations
- 3) a well-trained and adequately funded workforce in all research disciplines; we can never be sure from which research discipline the breakthrough will come that will solve a practical problem
- 4) global research efforts, both collaborative and competitive, that help to move research forward.

This new journal, *The Innovation*, is international and multidisciplinary, incorporating both science and technology. I do believe that publication of this journal will encourage the collaborative programs of outcome-focused research (Figure 1). I look forward to seeing

these outcomes crystallized in the papers published in the journal over the coming years.

### Declaration of Interest

The author holds patents relevant to the HPV vaccines mentioned in this article and receives royalties from sale of these HPV vaccines.

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