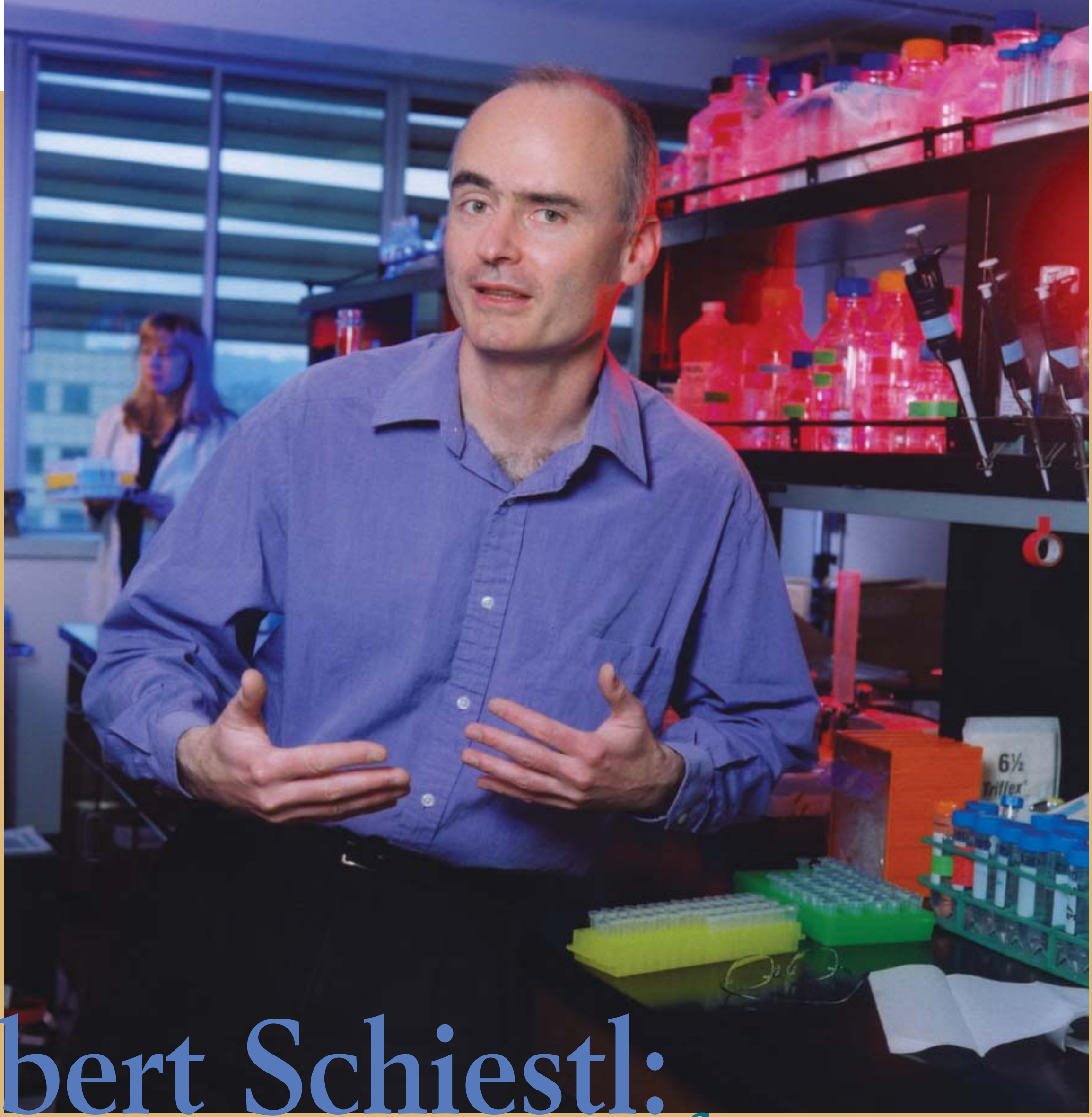
The director of UCLA's initiative to study gene-environment interactions says the wide-ranging expertise and culture of collaboration make UCLA the ideal place to carry out the effort.



Robert Schiestl: Center of Attention

As a Ph.D. student in Vienna, Austria, in the early 1980s, Robert H. Schiestl read newly published studies describing for the first time how exposure to certain chemicals could cause genetic instability – damaging DNA, the blueprint for life, and starting the cascade leading to cancer. Two decades later he heads UCLA's new Center for Environmental Genomics, which takes a far more sophisticated approach to the topic of our genes, what affects them, who's at risk and what can be done to protect susceptible groups – using tools that would have seemed the stuff of science fiction when Schiestl was starting his career.

So much has happened in the last 20 years, not the least of which was the sequencing of the 30,000 human genes and the development of methods to rapidly screen large numbers of them at once for mutations. "Today we know a lot more about genetic factors that help us to avoid DNA damage, as well as the DNA repair mechanisms," Schiestl says. During this period of rapid advance, Schiestl weighed in with his own seminal contribution: further characterization of types of genetic instability, and the development of methods to screen large numbers of chemicals for potential carcinogenic effects – tests of considerable interest to pharmaceutical companies.

The Center for Environmental Genomics, based in the School of Public Health, brings together faculty from many parts of the UCLA campus. The goal is to characterize the molecular processes by which occupational and environmental agents cause subtle changes in DNA that can lead to disease, and why certain sub-populations are more prone to harm from particular exposures than others. This knowledge will help center researchers develop "biomarkers" that indicate exposure levels, identify high-risk groups, and design strategies to prevent disease in these susceptible populations.

The center is addressing questions that couldn't have even been asked when Schiestl was completing his Ph.D. in biology and genetics at the University of Vienna, and yet his 6,000-mile journey to the Westwood campus has followed a logical path. "I was always interested in genetics and the biological effects of xenobiotics – external chemicals – in humans," he says. It's a theme that goes back to his doctoral thesis, which focused on the cancer-causing effects of the foreign substances. "I wanted to try to understand how cells become genetically unstable, which is a mechanism for carcinogenesis," he says. "Why do they become increasingly unstable in successive rounds of reproduction, finally metastasizing to other parts of the body? And what is the initial insult that makes this happen? I thought understanding that could be a key in preventing cancer."

Shortly after receiving his Ph.D. in 1983, Schiestl came to North America, first to the University of Alberta in Canada and then to the University of Rochester, where he joined the biology department as a postdoctoral fellow. After more than three years there and two at the University of North Carolina at Chapel Hill, he landed at the Harvard School of Public Health, where he spent nearly a decade before being recruited to UCLA in 2000.

At Harvard he continued to tackle the issue of genetic instability, including the interaction between environmental agents and genetically predisposing factors. Most significantly, his research group developed tests in yeast, human cells and mice that detect chemicals which trigger cancer-causing mutations – specifically, DNA deletions – as well as those that don't cause mutations but are nonetheless carcinogenic. "We were building on the knowledge that mutations which cause a high frequency of genetic instability often predispose to a high risk of cancer," Schiestl explains, "and also that a class of chemicals do not cause mutations but can cause cancer." Some of these assays are now being used by drug companies to screen for potentially cancer-causing chemicals.

The assays provide an invaluable research tool not only for determining whether compounds that might come into human contact are carcinogens, but also for investigating the interplay between environmental exposures and particular genes – and how damaged DNA can be repaired. "We can determine the effect of these exposures on the frequency of deletions, and then, for example, if we find that a chemical causes oxidative stress in mice, we can treat them with anti-oxidants to see whether that makes a difference," Schiestl says. "We can see whether a nutritional or drug intervention could reduce the frequency of deletions in genetically predisposed mice who are exposed to air pollution, or to cigarette smoke."

Schiestl's arrival at UCLA three years ago came at a time when the research tools for determining gene-environment interactions – including techniques for measuring the expression level of large numbers of genes in response to a given environmental exposure – were just coming of age. "The technologies have really matured," he says. "I used them at Harvard, but on a much smaller scale. With the sequencing of the human genome, they are becoming more and more available."

There are other reasons his research has benefited from the move west, he adds – reasons that have nothing to do with the technology, or the weather. "The scientific culture here is very interactive, very collaborative," he says. "And at UCLA, you have so much expertise in so many different disciplines, all on one campus. In this field, you need to bring together experts in many areas – epidemiology, toxicology, chemistry, molecular biology, genetics, biostatistics and others – to make progress." The interdisciplinary and broad-based nature of Schiestl's work is reflected in his appointments in three departments: environmental health sciences within the School of Public Health, and pathology and radiation oncology within the School of Medicine.

The Center for Environmental Genomics was established earlier this year, and its director clearly is a strong believer in the potential for making a major public health impact through the center's research. His excitement is evident as he leans forward in his chair and offers a visitor the example of beryllium disease to illustrate the point. Beryllium is an extremely lightweight and hard metal used in many industries, including aerospace and weapons production, he explains. A small percentage of workers exposed to dust or fumes from beryllium metal develop the lung disease. "The majority of the population is not sensitive to beryllium," Schiestl notes. "But it's been found that people with a certain polymorphism – a single genetic change – are extremely sensitive. And they would never know it unless they worked in a beryllium factory.

"The idea is to identify people's genetic predispositions and the environmental factors to which they are sensitive so that they can make an informed decision, in this case about whether to keep working in that factory. People can't change their genetic predispositions, but they *can* change their environment."

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—Dr. Robert Schiestl