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Klaus Bister *Editors*

Viruses, Genes, and Cancer

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Viruses, Genes, and Cancer

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Preface

In this special volume of *Current Topics in Microbiology and Immunology (CTMI)*, the scientific chapters are focused on current research developments in the fields to which Peter Vogt made preeminent contributions: viruses, genes, and cancer. Several chapters specifically highlight virus-host interactions, the role of infectious agents in human cancer, or HIV-host interactions relevant to pathogenesis and cure. Other chapters review the pivotal role of oncogenes and tumor suppressor genes as major cancer drivers—such as *MYC*, *RAF*, *PI3K*, or *TP53*—or explore the emerging role of microRNAs in tumorigenesis and cancer therapeutics.

Peter Vogt was born on March 10, 1932, in Broumov, a town with a large German-speaking population at that time, located in a region of the former state of Czechoslovakia that is now part of the Czech Republic. In 1950, Peter crossed the border from East to West Germany and moved to the City of Würzburg, where he received a B.S. in biology from the University of Würzburg in 1955. It was in this city that he also took classes with the painter Josef Versl. In 1955, he joined the Max-Planck-Institute for Virus Research (now: MPI for Developmental Biology) in Tübingen for graduate studies, and obtained a Ph.D. degree from the University of Tübingen in 1959. Peter then moved to the United States, to work as a Damon Runyon Cancer Research Fellow in the laboratory of Harry Rubin at the University of California in Berkeley from 1959 through 1962. Peter was Assistant and Associate Professor of Pathology at the University of Colorado School of Medicine at Denver from 1962 to 1967, and Associate Professor and Professor of Microbiology at the University of Washington School of Medicine in Seattle from 1967 to 1971. He then moved to Los Angeles to become Hastings Distinguished Professor of Microbiology and Chairman of the Department of Microbiology at the University of Southern California School of Medicine. Peter has been a Professor in the Department of Molecular and Experimental Medicine (now: Department of Molecular Medicine), The Scripps Research Institute, in La Jolla since 1993, serving as Executive Vice President for Scientific Affairs at this institution from 2012 through 2015. He is a member of several prestigious academies, including the US National Academy of Sciences and the German National Academy of Sciences Leopoldina. He has received numerous awards and prizes, including the Ernst Jung

Prize for Medicine, the Paul-Ehrlich and Ludwig-Darmstaedter Prize, the Pezcoller Foundation-AACR International Award for Cancer Research, and the IHV Lifetime Achievement Award for Scientific Contributions.

Throughout his scientific career, Peter has continued to make outstanding contributions to virology and cancer research. In his early work, he studied mechanisms of virus-host interactions, specifically avian retroviral cell entry, leading to a comprehensive definition of host range determinants. His focus then shifted to the genetics of retroviruses and the mechanisms of virus-induced cell transformation. This work culminated in the determination of the genetic map of Rous sarcoma virus (RSV), in the isolation of temperature-sensitive mutants of RSV, and in the first physical identification of a cancer gene, the oncogenic principle (v-*src*) of RSV, reported together with Peter Duesberg from the University of California at Berkeley in a seminal 1970 *PNAS* paper. The search for the origin of v-*src* led to the landmark discovery of the cellular origin of retroviral oncogenes by Harold Varmus and Mike Bishop from the University of California at San Francisco, in cooperation with Peter, recalled in the accompanying essay. Work in Peter's lab led to the identification of several retroviral oncogenes whose human cellular homologs (proto-oncogenes) are now recognized as major cancer driver genes, including *MYC*, *JUN*, and *PI3K*. Recent work in Peter's lab is focused on human cancer genetics, including the definition of tumor-specific mutations in cancer driver genes. Peter's research is also aimed at the isolation of inhibitors of oncogene protein products, such as MYC, eventually leading to the development of drugs suitable for pharmacological cancer treatment.

We are honored to act as volume editors for this very special issue of *CTMI* in appreciation of Peter Vogt, an eminent virologist and cancer researcher, and long-time editor of this series. Both of us had the privilege to work as post-doctoral fellows in Peter's lab in Los Angeles in the nineteen seventies, and we actually overlapped for some time. We vividly recall the exciting spirit, the collaborative atmosphere, and the scientific rigor of the lab at that time. Peter led by example and was at the microscope most mornings reviewing the results of experiments he had planned for that week. Lab meetings held at his home up on the Pasadena Hills were a time for stimulating scientific discussions, great food prepared by Peter, and an introduction to wonderful German wines! We also gladly remember the informal but tremendously stimulating West Coast Meetings of the Vogt, Bishop/Varmus, and Duesberg labs, held alternately in L.A. or San Francisco. Having worked with Peter was formative for our scientific careers, and we are very grateful. He has been a wonderful mentor and friend over the years. We also thank all authors of this volume for their great contributions.

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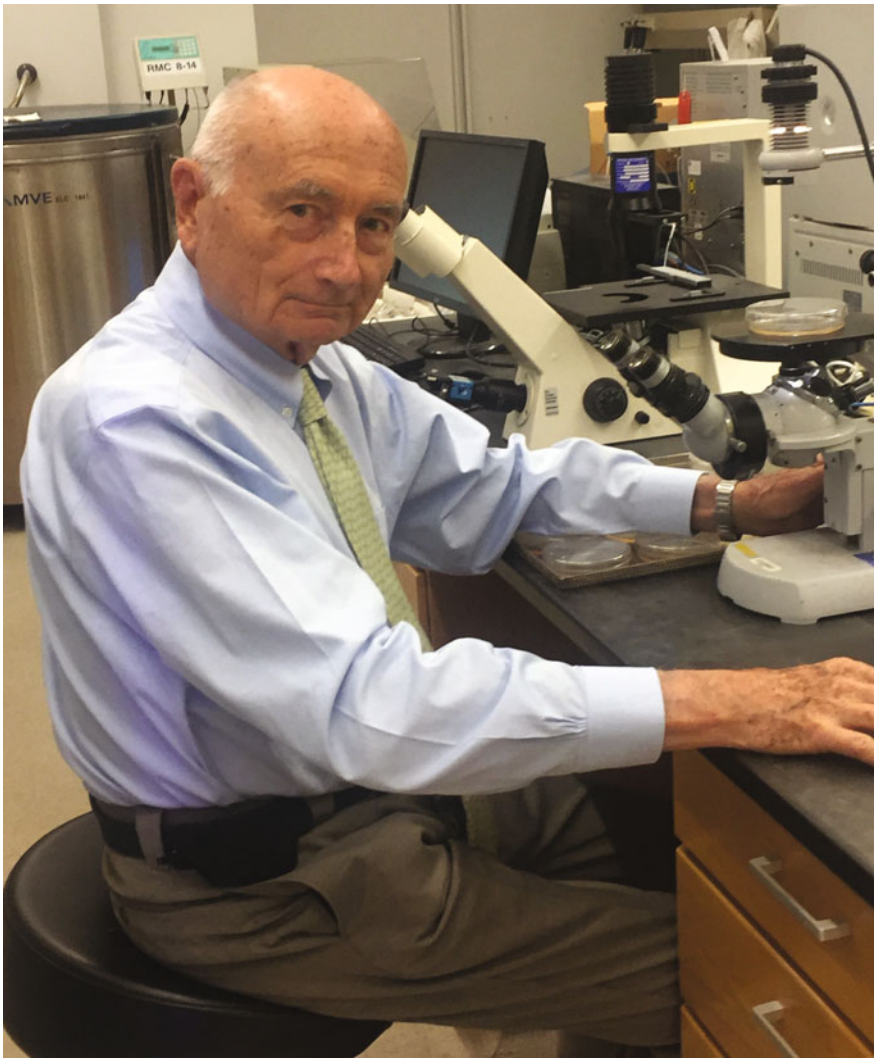
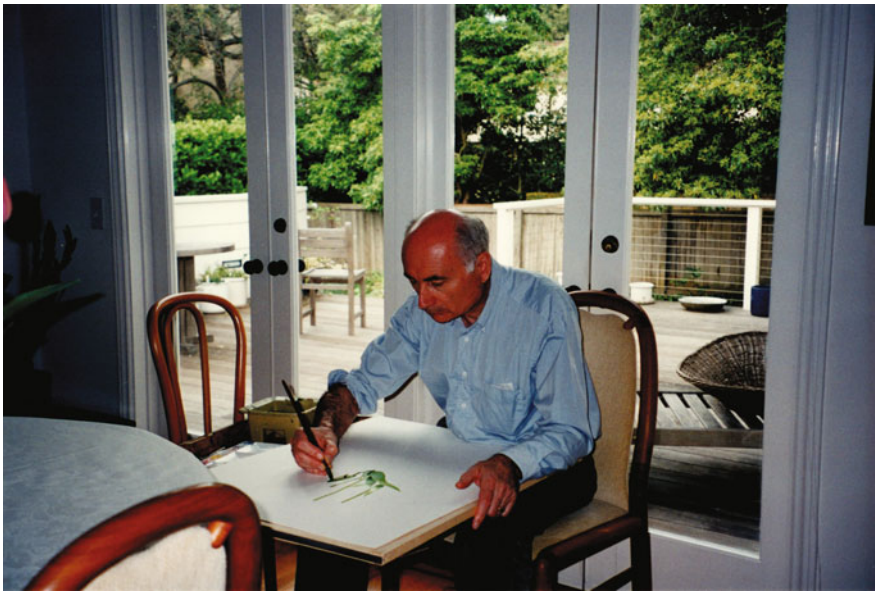
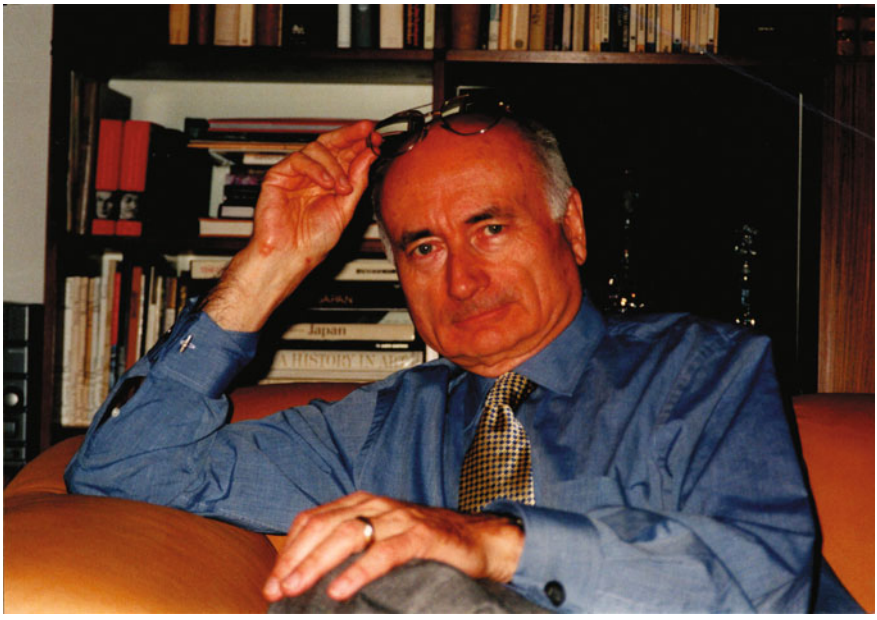


Peter K. Vogt




Japan

A Brief Homage to Peter Vogt

This volume celebrates Peter Vogt's remarkable service as an editor of *Current Topics in Microbiology and Immunology*. An astounding feature of his tenure is its length. We have known Peter well for a very long time—over forty-five years—yet he was already half a decade into his editorial duties at *CTMI* by the time we were introduced to him in the early 1970s.

That introduction came about in the best possible way: through mutual interests in combining different kinds of information and methods to do experiments that would probably otherwise not be done. The two of us and our colleague Warren Levinson first wrote to Peter in 1971, in a rather formal letter on UCSF letterhead, to ask for biological materials that might allow us to understand some peculiar features of the reassociation kinetics of the in vitro products of reverse transcription by Rous sarcoma virus (RSV). About the same time, two of Peter's senior post-doctoral fellows, Robin Weiss and Robert Friis, had written to ask if we'd be willing to use molecular probes to seek endogenous RSV-related proviruses in DNA from unusual birds.

From these simple (and initially not particularly productive) beginnings, our research team in San Francisco developed a long-standing relationship with Peter and his trainees (who had just moved from Seattle to Los Angeles)—a relationship that proved to be essential to much of our own later success and was from the start both scientifically stimulating and socially enjoyable. At the time, it was also recognized as unusual. Now we can see that it was an important forerunner of the kinds of "team science" and "multi-disciplinary" projects that are widely embraced today.

What was at first an occasional meeting between Peter's laboratory at the University of Southern California and ours at UCSF expanded gradually over the next decade to include many other RNA tumor virologists and their students and fellows—at first, from UC Berkeley; later from Cal Tech, UC Irvine, the Salk Institute, UC San Diego, and occasionally the Fred Hutchison Cancer Center. Regionally constrained by the lack of today's digital technology and dependent on a willingness to travel regularly to California campuses (fostered by miniscule fares on the slightly louche and long-since deceased airline PSA), this loose consortium,

now remembered as the West Coast Tumor Virus Cooperative, evolved over the ensuing decade to think together about virtually any aspect of RNA tumor virology. Focused initially on RSV, the topics eventually spanned a wide variety of retroviruses and exploited experimental tools that ranged from biological and genetic assays in cell culture to electron microscopy and molecular dissection of viral genomes. The discussions were unusual, even at that time, and particularly useful because the participants were generally willing, even eager, to share raw data not yet in manuscript form.

Peter provided the intellectual cornerstone of these meetings, even as the subjects and methods diversified, because he was the person most securely grounded in the foundations of our field. As emphasized elsewhere in this volume (in a brief biography by Klaus Bister and Eric Hunter), Peter grew up intellectually at a time—in part, during his training with Harry Rubin in Berkeley; in part, through his own labors in Seattle—when quantitative biological assays for replication and transformation by RSV and its cousins were being developed. These fundamental methods made the genetics and the molecular biology of tumor viruses not just possible but meaningful. Those of us who trained by studying other problems—and had an orientation that ran the risk of valuing the molecular over the biological—came to depend upon Peter's familiarity with the history of retroviruses and their biological properties in the design of our own work. Such lore is essential for experimental success, and it can be learned more easily from generous practitioners than from published work. For this reason, some of the moments we most vividly remember from the meetings of our research collective occurred during Peter's expositions on the genealogy, phenotypic effects, and genetics of RSV. His ability to draw simple messages from a decade or two of papers peppered with arcane terminology encouraged clear thinking and inspired all of us to conceive more meaningful experiments.

Meetings of the West Coast Tumor Virus Cooperative were occasions devoted to two principal purposes: to exchange new findings with other members and to discuss collaborative experiments. Our relationship with Peter and his group began with some immature ideas about joint projects, and the ideas deepened and proliferated over the ensuing decade. The best-remembered parts of our work together will inevitably be those that led to what is generally viewed as the most important outcome: the discovery of the first proto-oncogene, c-*src*. A fundamental feature of those experiments was Peter's provision of the ideal genetic reagents for them: clones of wild type RSV, fully competent for replication and transformation, from the Bratislava 77 strain and non-conditional, transformation-defective deletion mutants derived from those clones. These mutant/wild type pairs allowed our group to prepare molecular probes that proved to be nearly perfect representations of the viral transforming gene, v-*src*. Thus they were ideal for seeking the gene's cellular progenitor. Furthermore, in the era that preceded molecular cloning, they were essential for experimental success. There was never any doubt that Peter would be a coauthor of the publication that announced the discovery of c-*src*.

In the years before the discovery of c-*src*, Peter had also taught us about the value of working with birds other than chickens as hosts for replication of RSV—especially ducks and quail, from which useful cells and DNA could be abundantly prepared and assayed without any confusion with the RSV-related proviruses found endogenously in most chickens. Thinking about those avian species, and yet other

birds and other animals, prompted our early studies of the conservation of the c-*src* gene, efforts that were critical to interpretation of our first findings at a time when molecular evolution was still in its infancy. Peter's work with cells from various species, including rodents, as hosts for RSV also allowed us to study important steps in the RSV life cycle—especially DNA synthesis during infection, proviral integration, several aspects of gene expression, and virus entry—revealing the influences of host cells on viral gene expression and virus production.

We look back with pleasure and take pride in the dozen or so papers that Peter co-authored with one or (more typically) both of us between 1972 and the mid-1980's, a collaborative effort that has been only rarely equaled for its persistence and productivity. Still, as is often true of collaborations that require investigators to overcome the barriers that separate different institutions and places, we eventually went in different directions scientifically.

But our affection and admiration for Peter have been lasting, in part because his laser-like focus on research belies a broader cast of mind, and our relationships have come to depend as much on cultural as on scientific commonalities of interest. He is an accomplished water colorist and pains-taking student of the visual arts, to the point of using opera glasses to examine the fine detail of brush work in paintings; one can only imagine how he views the current mania for accumulating smart-phone photographs of museum displays without so much as a glance at the real thing. As his career began to take him to far-flung places, he fell head-over-heels for the culture of Japan—its people (one of whom he eventually married), traditions, cuisine, arts, and crafts. His pursuit of this passion has been characterized by the depth of scholarship, meticulous attention to detail and appreciation of history that have distinguished his career as a scientist.

Peter's celebratory watercolors inscribed to us and dispatched to our homes on October 9th, 1989 (see illustrations) remain among the most generous and meaningful tributes that we received after our Nobel Prize was announced on that day. So it is gratifying for us to be able to reciprocate now by offering this belated (and less colorful!) tribute to Peter on the occasion of the golden anniversary of his dedication to scholarship as an editor of *CTMI*.

San Francisco, USA J. Michael Bishop
New York, USA Harold E. Varmus

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Exchange of Genetic Sequences Between Viruses and Hosts

Robin A. Weiss

Abstract Although genetic transfer between viruses and vertebrate hosts occurs less frequently than gene flow between bacteriophages and prokaryotes, it is extensive and has affected the evolution of both parties. With retroviruses, the integration of proviral DNA into chromosomal DNA can result in the activation of adjacent host gene expression and in the transduction of host transcripts into retroviral genomes as oncogenes. Yet in contrast to lysogenic phage, there is little evidence that viral oncogenes persist in a chain of natural transmission or that retroviral transduction is a significant driver of the horizontal spread of host genes. Conversely, integration of proviruses into the host germ line has generated endogenous retroviral genomes (ERV) in all vertebrate genomes sequenced to date. Some of these genomes retain potential infectivity and upon reactivation may transmit to other host species. During mammalian evolution, sequences of retroviral origin have been repurposed to serve host functions, such as the viral envelope glycoproteins crucial to the development of the placenta. Beyond retroviruses, DNA viruses with complex genomes have acquired numerous genes of host origin which influence replication, pathogenesis and immune evasion, while host species have accumulated germline sequences of both DNA and RNA viruses. A codicil is added on lateral transmission of cancer cells between hosts and on migration of host mitochondria into cancer cells.

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