Editorial

William H Prusoff dies at 90 – a renaissance man that revolutionized the treatment of herpesviruses and HIV

Raymond F Schinazi*

*Corresponding author e-mail: rschina@emory.edu

William H Prusoff, a member of the Yale University School of Medicine faculty for 57 years and the godfather of modern antiviral chemotherapy, passed away on 3 April 2011. Best known for his seminal work on nucleoside synthesis and identification of the anti-HIV properties of stavudine (d4T), his discoveries yielded some of the most exciting selective antiviral agents, transforming the field and challenging scientific dogma. The concepts he brought to light now appear in a host of virological textbooks and have laid the foundation for key discoveries in the field.

Born 25 June 1920 in Brooklyn, New York, Bill Prusoff (Figure 1) was the son of Jewish Russian immigrants. The family moved to Miami in the late thirties because they were alarmed by the rise of pro-German sentiment and Nazi sympathizers in Queens. Bill graduated from the University of Miami with a degree in chemistry in 1941 (there was no such thing as a degree in Biochemistry in those days) and, unable to serve in the military in World War II because of vision problems, spent the war as a munitions inspector in Memphis and a water quality tester for troops stationed in Miami. After the war, he obtained a PhD in chemistry at Columbia University in 1947 and did his post-doctoral work in the laboratory of Arnold Welch at Case Western Reserve in Cleveland.

When Welch was recruited to Yale to head the pharmacology department in 1953, he brought Prusoff with him. Prusoff soon synthesized one of the first nucleoside analogues (5-iodo-2′-deoxyuridine), a compound that no one thought could be made because the synthesis involved the use of nitric acid, which would degrade the parent natural nucleoside 2′-deoxyuridine. This nucleoside analogue, the first clinically used antiviral drug, found widespread use as a preventive and treatment of herpesvirus keratitis. Yale never patented this invention, but this sight-saving discovery allowed Bill to garner NIH funding for many decades. Prior to the synthesis of this drug, it had been thought impossible to develop effective, non-toxic antiviral agents. For this seminal work, Prusoff has been called ‘the father of antiviral chemotherapy’ a title which he played down, simply stating that he had been lucky to pursue his passion for more than 50 years. “I don’t consider it work,” he said. “My work is my hobby.”

In the 1980s, the AIDS epidemic was raging and was shown to be caused by a novel retrovirus, human immunodeficiency virus (HIV). Prusoff and his late Yale colleague Tai-Shun Lin, with help from our laboratory at Emory University, showed that a failed cancer compound was active against HIV. Initially, Bill and Dr Lin called the compound dddddT, which was a mouthful, so we shortened it to d4T. After securing patents for d4T, Yale licensed them to Bristol–Myers Squibb. d4T was commercialized as Zerit and soon became a component of the first combination drug therapy for HIV. Millions of people worldwide have been treated with d4T and the AIDS epidemic was slowed until more effective drug combinations were developed. This drug generated huge revenues in royalties for Yale, far surpassing the amount generated by all of its other licensed medicines combined. However, it was not all about money; it was about saving lives. Nevertheless, the funds received allowed numerous new construction projects on campus and the renovation of superb modern laboratories in the Pharmacology Department in the Sterling Hall of Medicine at Yale.

Prusoff was the recipient of numerous awards, including the Peter Parker Medal, the highest award from the Yale School of Medicine, and the inaugural Lifetime Achievement Award from the Yale Comprehensive Cancer Center. In 1982 he was awarded the Experimental Therapeutics Award from the American Society of Pharmacology and Experimental Therapeutics and in 1988 was the recipient of the first award given by the International Society for Antiviral Research (ISAR). In 1989 he received an Honorary Degree from the University of
Cagliari, Italy, and in 1991 received the Medicinal Chemistry Award from the Société de Chimie Thérapeutique. Instituted in 2005, the William H Prusoff HEP DART Lifetime Achievement Award is given at each HEP DART conference to a researcher who has made integral contributions over their career toward the advancement of care of persons infected with hepatitis viruses. A similar award named the William Prusoff Young Investigator Lecture Award is given each year by ISAR. His many friends and colleagues nominated him for the Nobel Prize in 1998 for laying the foundations for selective phosphorylation of nucleoside analogues by the viral thymidine kinase/thymidylate kinase. When asked, Prusoff said his greatest satisfaction was that his discoveries helped people. “It’s a terrific kick for one’s ego,” he said. “Dr Lin and I got tremendous satisfaction from knowing that what we had produced was of benefit to society.”

In addition to his landmark scientific contributions, Prusoff was known for his generosity. Under his direction, the William H. Prusoff Foundation supported numerous programmes, including the Yale Initiative for the Interdisciplinary Study of Anti-Semitism (YIISA). He also endowed several lectureships in virology and pharmacology at Yale, funded several scientific prizes and supported the research of several individuals and laboratories at Yale. When Doctors Without Borders and Yale students called on the University and Bristol–Myers Squibb to make Zerit available at low cost in impoverished areas of the world, Prusoff actively joined in the campaign. “We weren’t doing this to make money,” he said. “We were interested in developing a compound that would be a benefit to society.”

Dr Prusoff’s work has affected virtually every antiviral application. The intrinsic clarity and creativity of his collective research has completely revolutionized the way we now develop antiviral agents. It is estimated that the annual economic growth of new antiviral agents is over 25%, easily surpassing all major medical research areas, including cardiovascular drug development. This growth is primarily attributed to Dr Prusoff’s lifetime work. The humanitarian aspects of his contributions cannot be overlooked, either, as the lives of countless millions of people have been beneficially impacted by the efforts of this modest gentleman scientist.

On a personal note, Bill was an inspiration to the many scientists he trained and nurtured, and he was passionate about inspiring young people to enter the scientific world and to make a positive difference. As a post-doctoral fellow arriving from England in 1978, Bill welcomed me to his laboratory and taught me everything I know about nucleoside chemistry and biology. By observing him, I learned not only how to run a lab but also how to become an entrepreneur scientist. To this day I lead my group at Emory by his example.

In Judaism, the Talmud teaches us that life is valued above almost all else. Judaism not only permits, but also often requires a person to violate any of the 613 commandments if necessary to save a life. Saving a single life is like saving an entire world. Bill and I were not religious, but we shared a common Jewish heritage. In 1996 Bill, Dr CK Chu, Dr A Nahmias and I successfully applied for an HIV National Cooperative Drug Discovery Program between Yale, Emory and University of Georgia. Through this collaboration, several landmark antiviral drugs were invented, including d4T, lamivudine (3TC) and emtricitabine (FTC), drugs that collectively have saved more than three million lives.

Bill’s stock of knowledge was unparalleled. He ‘assumed we knew nothing, but that we had infinite wisdom’. He taught us not to just climb the mountains – but to conquer them. He taught us to always aim above other people’s expectations and outperform, and through education and science leave the world a better place than it is now. He inspired us by being optimistic even in the worst of times by saying ‘the best is yet to come’ and ‘a good story is always worth repeating’. And yes, he did love to repeat his stories to anyone who would listen!

We will all miss him, especially his daily email jokes and good sense of humour. I loved Bill Prusoff – my mentor, friend and colleague – may he rest in peace.