Arthur D. Riggs 1939–2022

A world-renowned diabetes expert and molecular biologist, Arthur (Art) Riggs pioneered the lifesaving recombinant protein and antibody drugs on which the biotech industry was built.

On 23 March, Arthur (Art) D. Riggs passed away at the age of 82 years. A pioneer in genetics and epigenetics, Riggs also made seminal contributions to biotechnology. The impact of his work shaped many areas of today's molecular biology and biomedical sciences.

Born in Modesto, California, a city with a name that mirrors his own character, Riggs spent his entire scientific career in Southern California. After earning his undergraduate degree from the University of California Riverside in chemistry, he received a PhD from Caltech, Pasadena, and continued with postdoctoral studies at the Salk Institute near San Diego. In 1969, Riggs was recruited to the City of Hope (CoH) Medical Center in Duarte, by the eminent geneticist Susumu Ohno, and became a member of the Division of Biology, which he later chaired until the year 2000. He served as the Director of the CoH's Beckman Research Institute, and until very recently, he was the Director of the new Diabetes and Metabolism Research Institute of the CoH, which has carried his name in his honor since 2021. In 2006, Art was elected to the National Academy of Sciences of the United States.

Riggs is known for at least four far-reaching scientific discoveries and accomplishments: (1) bidirectional DNA replication; (2) developing a concept for the mechanism and function of mammalian DNA methylation; (3) the first to clone and express recombinant human genes; and (4) technology for generating recombinant antibodies.

In the late 1960s, along with fellow Caltech graduate student Joel Huberman, Riggs discovered that DNA in mammalian cells is replicated using multiple origins of replication in a bidirectional manner from a fork-like growing point[1]. Remarkably, the two students designed and performed these experiments on their own; neither thesis advisor appeared as authors on this seminal paper. Riggs later applied this concept of 'independence' to his own graduate students[2].

In the 1970s, Riggs played a key role in launching the field of modern epigenetics. Inspired by his earlier studies on the Lac repressor in bacteria[3,4], Riggs had become fascinated with DNA modifications, recognizing that these modifications may interfere with protein–DNA interactions, perhaps best exemplified by the bacterial restriction and modification systems. In a landmark conceptual paper published in 1975 (ref. [5]), Riggs proposed that in mammals, patterns of DNA methylation, which exist chiefly in the form of 5-methylcytosines at CpG dinucleotide sequences, can be faithfully copied during DNA replication by a DNA methyltransferase (DNMT1). This enzyme maintains fully methylated CpG sites by acting preferentially on hemi-methylated intermediates arising shortly after DNA replication. He also proposed that DNA methylation sites could control gene expression by interfering with the binding of regulatory proteins and could be involved in X-chromosome inactivation. Therefore, the heritability of DNA methylation provides a mechanism for maintaining epigenetic states during cell divisions. All these predictions turned out to be correct. A conceptually similar proposal for DNA methylation maintenance during replication was developed independently by Holliday and Pugh and published in that same year[6].

Arthur Riggs made many contributions that benefit mankind both inside and outside the lab. Credit: City of Hope

Throughout his career, Riggs demonstrated a keen sense for recognizing and driving forward what became key molecular biology technologies. During his early days at the CoH, Riggs conceived how foreign genes could be expressed in bacteria based on his research on the *lac* operon and was one of few scientists who realized that synthetic DNA could be a useful tool in molecular biology in general. This early work led to the cloning and expression of functional *lac* operator DNA in bacteria[7].

To accomplish these goals, Riggs teamed up with one of us (K.I.), a DNA chemist. In collaboration with Herb Boyer (of the University of California, San Francisco) and the fledgling biotech company Genentech, we successfully expressed the synthetic gene encoding somatostatin, a peptide hormone, in *Escherichia coli*[8]. Riggs was the scientific leader of the team, and much of the work was carried out at the CoH, as Genentech's labs were not yet completed. Somatostatin was the first human-designed and -made gene that functioned in any organism[8,9]. This groundbreaking accomplishment jump-started the biotech industry.

Soon after, using the same concept, the CoH team in collaboration with Genentech scientists produced human insulin in bacteria[10]. This procedure provided unlimited amounts of human insulin and replaced bovine insulin for treating diabetes patients. The US Food and Drug Administration approved human insulin (Humulin) in 1982 as the first protein therapeutic product based on recombinant DNA technology[11]. Following this success, a variety of peptides and proteins, which were either difficult to obtain in sufficient quantity or were not available, could be produced for the treatment of human diseases.

Riggs immediately recognized the potential of genetic engineering for producing recombinant antibodies. In 1980, on a trip to Israel, he recruited Shmuel Cabilly to join his lab as a postdoctoral fellow. Collaborating with Genentech, they developed the first recombinant antibodies. The recombined heavy and light chains of an anti-CEA (carcinoembryonic antigen) immunoglobulin G expressed in *E. coli* successfully bound CEA[12]. This work laid the foundation for making recombinant antibodies, which created another valuable tool for the biotech industry. Although the majority of recombinant antibodies are now made in mammalian cells, this seminal work demonstrated the power of engineering heavy and light chains to generate immuno-active antibodies. The famous Cabilly patents, filed in the 1980s and co-owned by the CoH and Genentech, cover the fundamental technology for making recombinant antibodies. The patents have been licensed to more than 70 biotech and pharmaceutical companies. They are linked to some of the most successful antibody-based drugs, including anti-HER2 (trastuzumab, Herceptin) and anti-CD20

Genetic engineering pioneers circa 1977. Keiichi Itakura (right) and Arthur D. Riggs (left) watch as data come in showing that they succeeded in producing an active human protein in *E. coli*. Credit: Stanart Photo

(rituximab, Rituxan). Although the insulin and recombinant antibody patents have now expired, these lucrative patents provided decades of strong financial support for the Beckman Research Institute of the CoH.

Although Riggs made many important contributions to translational research that helped spawn and expand the biotech industry, one of his most cherished and longstanding scientific interests remained DNA methylation research and epigenetics. When two of us (J.S.-S. and G.P.) joined his laboratory, we worked on the role of DNA methylation and protein–DNA interactions in the process of X-chromosome inactivation[13,14]. X inactivation remains a prime example of a truly epigenetic pathway.

Riggs was not only a great leader and generous mentor; he also was an adventurous and fun friend. We have many wonderful memories of whitewater rafting trips and our annual 'death march' in Joshua Tree National Park. Riggs would lead a group of brave individuals into the forbidding desert landscape and would then (intentionally?) get lost. Although he benefited from his patents personally, he lived modestly, donating a large fraction of this income to charity, including the CoH. He and his wife, Jane, cared deeply about protecting the environment and did a lot in this fight. They weeded invasive plants in the California deserts, supported research to find the best locations for sun-energy collection, and purchased lands for the Nature Conservancy. Riggs was a visionary leader, a man full of wisdom, who paved the way for many areas of biology that have impacted genetics, epigenetics and the development of essential and effective clinical therapies that greatly benefit humankind. ❐

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