George McDonald Church (1954- ) [1]

By: Rojas, Christopher Schnebly, Risa Aria Keywords: genome sequencing [2] history of genetics [3]

George McDonald Church is a geneticist who has helped develop numerous technologies to sequence and edit DNA throughout the twentieth and twenty-first centuries in the US. DNA is the genetic information in every living organism that encodes the instructions for life and all its processes. Church made understanding the genetic code easier by developing technologies like multiplex sequencing and using them to aid projects such as the Human Genome Project and the Personal Genome Project. He also developed Multiplex Automated Genome Engineering, a technique that allows researchers to easily edit genetic code, which can change an organism’s traits and overall function. As of 2021, Church is involved in multiple endeavors using genome [4] engineering to create new biofuels, reverse human aging, and revive extinct species through a process called de-extinction. Church’s work has made it easier for scientists to understand the sequence and function of genomes and to edit organisms’ genomes to produce completely novel functions.

Church’s career has largely centered around developing techniques to sequence and edit different organism’s genomes, or their full set of DNA. DNA is made up of two strands connected by small molecules called nucleotides. The order of the nucleotides in an organism’s DNA dictates how it will develop and function. Genome sequencing, which determines the order of nucleotides in an organism’s DNA, can help researchers understand how and why an organism develops and functions the way it does. Genome editing techniques, on the other hand, enable researchers to add or remove nucleotides in the genome [4] to alter the instructions for an organism’s development. Changing even just one nucleotide in an organism's genome [4] can produce dramatic effects. Genome editing has many potential applications, from helping to develop new treatments for diseases, making compounds that can be used for fuel or medicine, changing an organism’s appearance, or even creating new organisms with novel functions altogether.

Church was born on 28 August 1954 to Virginia Anne Strong and Henry Stewart McDonald III. His father was a lieutenant in the United States Air Force, and Church was born on MacDill Air Force Base near Tampa Bay, Florida. When Church was three years old, he was put up for adoption and taken in by Peyton Jordan. In 1963, Church was again put up for adoption. That time, Gaylord Church adopted and raised Church. Church reported that he spent most of his childhood reading to find answers to the questions he had about the world around him. In one interview, Church discussed how he was fascinated by insects [8], and would rush to the library to learn more about their metamorphoses after watching them change. Church also stated that he was fascinated with computers at a young age. Home computers were not yet widely available for the public when he was a child, so Church learned to build a functional home computer at the age of ten in 1964. He completed high school at Phillips Academy in Andover, Massachusetts, in 1972. There, he mastered multiple programming languages that researchers had only just recently invented.

Church then completed undergraduate degrees in zoology and chemistry in 1974 at Duke University in Durham, North Carolina, in just two years. During his time there, he began studying RNA, or ribonucleic acid, a class of molecules essential to the functioning of cells. After obtaining his undergraduate degrees, Church pursued his doctoral degree in biochemistry also from Duke and found work as a research assistant to professor Sung-Hou Kim, a biophysicist who researched structures of biological molecules in the 1970s. In Kim’s lab, Church used X-ray crystallography, a technique that scientists use to study the structure of proteins and biological molecules, helping them to understand how the nucleotide bases in a transfer RNA molecule are related to the molecule’s structure. Church and his coworkers later published findings in what became Church’s first peer-reviewed publication, “Secondary Structure Complementarity Between DNA and Proteins,” published in the journal Proceedings of the National Academy of Sciences [9] in 1977. However, Church spent so much time in the lab rather than on his classwork that he was expelled due to failing grades in 1976.

Church then applied to Harvard University [7] in Cambridge, Massachusetts, and was accepted in 1977. In 1984, Church completed a PhD at Harvard in molecular biology while developing a genome [4] sequencing technique as part of his dissertation. At Harvard, Nobel Prize recipient Walter Gilbert [8] advised Church’s dissertation research. At the time, researchers attempted to sequence DNA by injecting it into bacteria and allowing the bacterial cell to replicate the DNA, but that process sometimes lost genetic information. Church and Gilbert developed a technique that improved the process.

Church continued to work with Gilbert after graduation at Biogen Research Corporation, a biotechnology lab in Cambridge where Gilbert moved many members of his former Harvard lab. Church stayed at Biogen for six months before moving to San Francisco, California, to be with his future wife, Ting Wu. Church found a post-doctoral position at the University of California, San Francisco, in San Francisco, California, in a genomics lab studying stem cells [9]. However, he only stayed at that position for a little over a year because in 1986, Church became an assistant professor of genetics at Harvard Medical School [10] in Boston, Massachusetts. While at Harvard in 1988, Church developed the method of multiplex DNA sequencing. Multiplex sequencing takes strands of DNA and gives them chemical tags before sending them through an automated DNA sequencing machine. The
machine can sequence multiple strands of DNA simultaneously, due to the chemical tags that the researcher attached. Multiplex DNA sequencing enabled scientists to be able to sequence a greater volume of DNA in a shorter amount of time, thereby reducing the cost of sequencing.

In 1990, the National Institutes of Health[^11] funded the Human Genome Project and appointed Church as one of the project’s architects. Church was one of the original scientists involved in the Project’s development from the beginning. The Human Genome Project was a concentrated effort to sequence and map the human genome[^4], which is over three billion nucleotide base pairs long. The National Institutes of Health[^11] funded the Project with the expectation it would lead to better understanding of human evolution[^12] and the origin of many human diseases. For example, understanding the human genome[^4] could enable researchers to identify mutations commonly linked with the development of cancer. The Project completed its full sequencing in April of 2003. However, even though it uncovered the number and order of nucleotides, there was much to learn about what functions those nucleotides had and what traits they encoded.

Continuing in the 1990s, Church’s personal and professional life progressed significantly. In 1991, Church and his wife Wu had their first and only child, a daughter named Marie Tai-lien Wu. Church’s professional life continued to develop, too. In the early 1990s, Church assisted in the development of an idea for another sequencing technique called nanopore sequencing that could help make sequencing quicker and more accessible for projects like the Human Genome Project. With nanopore sequencing, researchers measure the change in electrical current at a nanopore, a channel only one nanometer in diameter, as each successive nucleotide on a DNA strand passes through it. A nanometer is a unit of length that is extremely small. For example, a strand of human hair is approximately 100,000 nanometers wide. Each kind of nucleotide registers a different voltage. As different nucleotides pass through the nanopore, researchers can easily discern which nucleotide is which and the order they are in.

Additionally, Church also began developing another sequencing technology called polony sequencing that enabled researchers to sequence millions of DNA strands at once. In conjunction, Church developed a commercially available sequencing machine that automated polony sequencing, the Polonator G.007, which made DNA sequencing about one hundred times less expensive than it had previously been. By the end of the decade in 1998, Harvard promoted Church to be a full professor of genetics in the medical school.

After developing those new sequencing techniques and completing the Human Genome Project, Church established the Personal Genome Project in 2005. Through that project, Church planned to provide an open source, open-access genome[^4] bank where the genome[^4] sequences of hundreds of thousands of volunteers could be publicly accessible. That database could serve as a place where scientists could access and compare multiple genomes in order to study genomic interactions with the environment, determine traits that the genome[^13] express, and to describe and explain the links between genes[^13] and disease. Church began the project by fully sequencing and mapping the genomes of ten volunteers, offering up his own genetic information as one of the first ten that his team sequenced. As of 2021, more than 10,000 volunteers have offered up their genetic information to the project.

In 2009, Church moved from sequencing genomes to editing them when he developed a new technology in collaboration with Harris Wang, a doctoral student at Harvard at the time, called Multiplex Automated Genome Engineering, or MAGE. MAGE enables researchers to edit an organism’s genome[^4] in multiple places at once. Before MAGE, genetic engineers could generally only manipulate one gene at a time and had to let each edited cell reproduce so they could have multiple copies of its genome[^4] before moving on to edit a different site in one of those same cells. MAGE drastically reduced the amount of time and money it took to create multiple genomic edits. That made genetic engineering more accessible, enabling more researchers to use the technology to treat diseases, create new organisms, or in Church’s case, create biofuels.

Church used MAGE in several projects where he manipulated a bacterial genome[^4] to produce a biofuel. In 2010, a California-based biotechnology company Church helped found called LS9 won the Presidential Green Chemistry Award for engineering bacteria to convert sugar into a diesel-like fuel. Also, a biotechnology firm under the management of Church called Joule Unlimited won the Wall Street Journal Technology Innovation Award for engineering photosynthetic bacteria in 2011. Once engineered, those bacteria could then convert sunlight, carbon dioxide, and water into a type of renewable fuel. Both fuels produced by those companies contain alkanes, which are molecules made of hydrogen and carbon that are compatible with automobile engines. The alternative fuels those companies make could be a sustainable option to fuel all kinds of vehicles, from cars to jets.

In 2012, Church became highly involved in promoting and working towards de-extinction, or a process that creates new proxies of extinct species through genetic engineering. That year, he published a book with Ed Regis titled Regenesis: How Synthetic Biology Will Reinvent Nature and Ourselves, in which the authors explore how biotechnology can make innovative new procedures possible, such as the creation of new renewable energy, the extension of human life, or the de-extinction of species. Also in 2012, Church used some of the technology he described in that book to help the newly created organization[^14] Revive & Restore launch[^15] projects to de-extinct the passenger pigeon and the woolly mammoth using genetic engineering. Church and his team aimed to edit the genomes of the species’ closest living relatives to resemble the genomes of the extinct species in order to create new hybrid organisms that look and function like the extinct ones. Church’s involvement with Revive & Restore extended beyond 2012 as he later began leading the organization[^14]’s Woolly Mammoth Revival project.
In 2013, Church was part of a team that conducted a study on CRISPR-Cas9, a genome editing tool derived from bacteria that can cut out and position specific DNA sequences to edit the genetic information of cells. Church’s team supported the notion that CRISPR-Cas9 was an efficient and reliable technology with which scientists could edit human genetic information. Church has also used CRISPR-Cas9 in much of his own research, in particular when conducting genetic engineering for de-extinction projects. In 2015, Church and his team of Harvard researchers announced that they had successfully copied several woolly mammoth genes into the genome of the Asian elephant. By 2017, the team announced that they had copied at least forty-five woolly mammoth genes into the elephant genome, making progress towards creating a mammoth-elephant hybrid that could replace the extinct woolly mammoth.

Through the late 2010s, Church continued to lead and collaborate on multiple projects using genetic engineering in novel ways. In 2017, Church launched a startup called Rejuvenate Bio that investigates the possibility of using gene editing technology to slow or even reverse aging. In 2018, the company announced they had successfully reversed several age-related diseases in mice and in 2019 the company began using gene therapy to try to treat age-related diseases in dogs. Additionally, in 2020, another one of Church’s companies called Nebula Genomics launched an at-home test that can sequence a person’s entire genome for the price of 299 US dollars, a steep drop since the days of the Human Genome Project when sequencing a whole genome cost billions.

Church’s work has helped scientists read DNA more efficiently and understand the link between genes and the phenotypes they encode, and promoted the development of gene editing technology that could be used to treat human disease, create biofuels, and even recreate extinct species. Church has published over 500 scientific articles and received dozens of patents. Church’s work spanned over twelve commercial enterprises using synthetic biology to produce, among other things, biofuels, synthetic photo-synthesizers, and pharmaceuticals. Church has also won over fifty awards over the course of his career and was elected as a member of the National Academy of Sciences in 2011 and the National Academy of Engineers in 2012. Additionally, the American Society for Microbiology awarded Church with the Promega Biotechnology Research Award in 2009 Microbiology, and the Franklin Institute, a science museum and research center in Philadelphia, Pennsylvania, awarded Church with the Bower Award and the Prize of Achievement in Science in 2011.

As of 2020, Church remains a professor of genetics at Harvard University and continues to reside in Massachusetts with his wife.

Sources

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