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Maynard Olson: a scientist's scientist, and recipient of the 2007 Gruber Prize for Genetics

Maynard Olson

Maynard Olson's latest research interest could change our approach to treating cystic fibrosis—that dread genetic condition in which victims normally die before they reach 40, as a result of chronic lung inflammation from a bacterial infection they acquired in early childhood.

Olson and his colleagues at the University of Washington Genome Center, where he is director, have been studying changes in the genome of Pseudomonas aeruginosa, the bacterium that causes the inflammation. They found it evolves inside the human lung in a relatively predictable way. The result is that the bug that ends up killing its human host has very different characteristics from the one which invaded decades, and many bacterial generations, before. The work could well lead to more effective therapy.

While Olson is aware of, and excited by, this practical outcome to the research, that's not why he became interested in it. As one of the fathers of genomics—mapping and studying the entire genetic material of organisms—he wanted to demonstrate how it could be applied. "The future lies in turning genomic methods into true experimental tools," he says, "so that we can use them in hundreds of small laboratories to solve real biological problems such as those posed by infectious disease." So, as he tends to do, he is showing the way.

Olson is a scientist's scientist, of the old school. He believes that if you take care of basic research, and study the fundamentals that make life and the world tick, then the applications of the science will take care of themselves. And he is suspicious of short cuts.

At one stage relatively early in his career, studying yeast to figure out how to map a genome, he worked for more than five years without publishing anything to show what he was doing: "I still had no map." He had made progress, however, and at the end of it all, somewhat to his surprise, the US National Institutes of Health (NIH) decided to fund him for another five years.

His approach has led him far. By following his interest in fundamental questions, he made several key discoveries that helped to set genomics on its feet. In particular, he pioneered essential links between genetics and the burgeoning field of information science, which made handling the enormous complexity of genomes tractable. And now, for his efforts, he has been awarded the 2007 Gruber Prize for Genetics.

"When he assembled his physical map of the yeast genome, he developed a new way to piece together the puzzle. He allowed us to mechanize, computerize and organize the process," says 2003 Gruber Genetics Laureate, David Botstein. "Maynard was one of the top two or three key brains behind the Human Genome Project (HGP). He is a mentor—not just for his students, but for whole institutes."

Perhaps it's not surprising Olson ended up such a science buff. He was born into a world steeped in science. His father was a medical researcher, and he grew up in Bethesda, Maryland, the company town of the NIH. "The family influence was enormous," he says. "I lived in an environment that encouraged following one's passions, and from the earliest age I was fascinated by the workings of nature." Hiking in wilderness is still a favorite pursuit.

Surprisingly he initially trained and worked as a chemist. "I wasn't even a biochemist. I was a pure, small molecule, inorganic chemist." But in his early 30s, while working at Dartmouth College, New Hampshire, he had what he calls an early mid-life crisis. "I still loved science, but I needed something altogether new to do."

What he had read about genetics stimulated him. It was 1974, the beginning of the recombinant DNA era, when molecular biologists first showed they could use enzymes to manipulate and engineer genetic material precisely. "I had no prior experience of biology or genetics, but I could see that this was being driven by a certain perspective of the physical sciences on natural processes, so thought I would give it a try myself." And he never looked back.

Olson took a sabbatical in the genetics laboratory of Benjamin Hall at the University of Washington in Seattle. "I had such a great time that I quit my job and stayed on for five years as a post-doctoral fellow." And during those five years most of the methods still used in handling DNA emerged. Researchers became preoccupied with isolating and studying individual genes.

But Olson could see further. By the time he left Seattle in 1979 to establish his own laboratory at Washington University in St Louis, Missouri, he was convinced that in order to determine how genes worked you needed an overview of what genes were present and where they were in the genome.

To investigate that idea Olson recognized one would have to analyze whole genomes. And whereas the DNA of individual genes involved molecular chains of tens of thousands of base pairs, even simple genomes like yeast contain tens of millions. It was a daunting task, but Olson could see that all the techniques were there.

The basic method was to break the DNA chain up into small random pieces, each of which could be cloned and sequenced. These small pieces of the jigsaw puzzle could then be compared and reassembled into the whole chain, taking clues from the places where they overlapped. This process was straightforward for short segments of DNA.

But the numbers of comparisons increased exponentially as the length of the DNA chain increased to the scale of a whole genome. Olson, however, was convinced it was possible. It was all a matter of scaling up. "The key idea, and the origin of genomics, was to turn such repetitive work into a linear

process."

Olson was able to do so with the help of the computer which, in the early 80s, was only just emerging from the era of punched cards. Throughout the 80s, he and Nobel Laureate Sir John Sulston worked independently and doggedly, developing algorithms for parallel genome mapping projects—Olson on yeast, Sulston on the nematode worm, *Caenorhabditis elegans*. They even published their first papers on their respective genome maps in the same issue of the Proceedings of the National Academy of Sciences in 1986. The science of genomics was beginning to take shape.

Then researchers began to discuss sequencing human and other very large genomes more than 100 times bigger than yeast. Olson quickly recognized that the techniques he had developed and used to map the yeast genome would never do for the human genome. The task was not impossible, he thought, it was just a matter of scaling up the techniques yet again.

And again he came through, with two significant methods that made the Human Genome Project possible. The first was the development of yeast artificial chromosomes, the forerunner of bacterial artificial chromosomes. This essentially involved using microorganisms to clone large chunks of DNA—increasing the size of the jigsaw pieces, and thereby reducing the number it took to cover a genome.

The other problem Olson solved had to do with information. The human genome was of such scale that it was always going to involve many different groups sequencing many different parts of the genome in parallel. The question was then how to check, compare and reference information emerging from any laboratories. Originally, it was thought that copies of the puzzle pieces, the clones on which the sequencing was based, would have to be stored centrally and transported to laboratories around the world. "At the time we thought half the project cost would go in transport," says Botstein. "The original plan included a large warehouse/distribution center in Chicago."

It was Olson who recognized that unique sequences of a few hundred base pairs each spaced throughout the genome—sequence tagged sites—could serve as reference points. Instead of sending chunks of DNA around the world, one could simply send information linked to these sites.

For more than a decade from 1992 until the project was completed in 2003, Olson served on various committees overseeing the huge endeavor. He became the unapologetic champion of what he calls "trying to do the thing right", and fought fiercely against "the pragmatic forces, who wanted to get the project done no matter what and were willing to make compromises".

With that phase of his life over, Olson, the philosopher scientist, is now at the forefront of research again, taking genomics out into the real world.

By Tim Thwaites and Niall Byrne
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