SYDNEY BRENNER

TOP THREE AWARDS

- Nobel Prize in Physiology, 2002
- Albert Lasker Special Achievement Award, 2000
- National Order of Mapungubwe (Gold), 2004

DEFINING MOMENT

To view the DNA model for the first time.

A LIFE DEDICATED TO SCIENCE

In the more than eight decades that Nobel Laureate, Prof Sydney Brenner, has all-consumingly devoted his life to science, he twice wrote powerful proposals of no longer than a page. Short but sweet, these kick-started the two projects that are part of his lasting legacy.

The first was to request funding to study a worm, because he saw in the nematode *Caenorhabditis elegans* the ideal genetic model organism. He was right, and received the Nobel Prize for his efforts. The other proposal, which set out how Singapore could become a hub for biomedical research, earned him the title of "mentor to a nation's science ambitions". Brenner's way of approaching a task or a problem is often atypical, but it bears much fruit. Former colleague David Lane explains in *Sydney Brenner: a Biography* by Errol C Friedberg: "Those who want things to be very structured and stable don't suit Sydney's personality very well. He's the sort of guy who enjoys tossing the hand grenade around. He asks the tough questions and if he sees things looking too settled and not moving forward in a new direction he stirs things up."

At the age of 89, Brenner has no inclination to retire. As ever, it is genomics and especially genome evolution that captivates him. This Senior Fellow of Singapore's Agency for Science, Technology, and Research (A*STAR) still leads a team of scientists building models to explain how induced pluripotent stem cells can be genetically developed into adult cell types. He also holds senior faculty positions at the Salk Institute and the Howard Hughes Medical Institute in the US.

"There is nothing more interesting and more exciting than being a working scientist," he explains. "I am thankful that although I have several physical disabilities my brain seems to have retained most of its capacity, and of course I am very much indebted to my doctors for keeping me going."

C. ELEGANS WORK

"To start with we propose to identify every cell in the worm and trace lineage. We shall also investigate the constancy of development and study its control by looking for mutants," is how Brenner ended his proposal on *Caenorhabditis elegans* to the UK Medical Research Council in October 1963. He was looking for a new challenge after already having helped to show that genetic code is composed of non-overlapping triplets and that messenger ribonucleic acid (mRNA) exists.

His first paper on *C. elegans* appeared in *Genetics* in 1974, and in all, the work took about 20 years to reach its full potential. In 1998, thanks to a research consortium in the UK and US, this soil organism became the first multicellular organism to have its complete genome sequenced.

The 2002 Nobel Prize for Physiology was awarded to Brenner and colleagues Robert Horvitz and John Sulston for their combined body of work. Their discoveries concerning the genetic regulation of organ development and programmed cell death opened up new avenues for biological and medical research. It provided new insights into the development of organs and tissues and why specific cells are destined to die, for instance during heart attacks and strokes. It also helped the understanding of how certain viruses and bacteria attack cells.

During the award ceremony, Prof Urban Lendahl of the Nobel Committee explained how Brenner took up the challenge to find a species that is simpler than humans, but is still sufficiently complex to allow for general genetic principles to be deduced.

Lendahl explained: "His choice was the nematode *Caenorhabditis elegans.* This may at first seem odd, a spool-shaped, approximately 1 millimeter long worm with 959 cells that eats bacteria, but Brenner realised in the early 1960s that it was what we today would call 'loaded with features'. It

was genetically amenable and it was transparent, so that even cell division and differentiation could be directly followed in the worm under the microscope. Brenner demonstrated in 1974 that mutations could be introduced into many genes and visualised as distinct changes in organ formation. Through his visionary work, Brenner created an important research tool. The nematode had made [it] into the inner circle of research."

SINGAPORE'S MENTOR

In Friedberg's biography, Brenner describes the succinct initial plan he drew up that would see Singapore's government finance cutting-edge research facilities in molecular and cellular biology from the early 1980s:

"Knowing that busy people don't like reading lengthy documents and mindful of Winston Churchill's famous admonition that he didn't like reading anything that was more than one side of a single sheet of paper, I wrote out a basic plan for the future on a half of one side of a single sheet of A4!"

This led to the opening of the Institute for Molecular and Cellular Biology (IMCB) at the National University of Singapore in 1987 to train Singaporeans and provide research infrastructure. A*STAR was established in 1991 to foster scientific research and talent in a knowledge-based economy. Since 2009, the Molecular Engineering Lab (MEL) at the Biopolis has provided space for recent PhD graduates to work without constraints within an interdisciplinary environment.

These endeavours have proven that Singapore, despite being a tiny population with little experience in basic research, can produce high-calibre scientific research. When Brenner accepted the Singapore National Science and Technology Medal in 2006, he said: "Here we now have hundreds, no thousands of young people devoted to science and to a career in biomedical research – and that's an opening to the new world."

Brenner enjoys iconic status in Singapore and is an honorary citizen of the country. There is even a hybrid named after him in the National Orchid Garden. In October 2015, a two-day event celebrated his pioneering work, and included the opening of an exhibition about him.

Amongst the most notable work of his IMCB research team is that on the fugu puffer fish (*Takifugu rubripes*). The fugu and human genomes share similar blueprints, even though the former is about eight times smaller than the latter. Like *C. elegans*, the compact fugu genome is an ideal model for studying larger and more complex genomes.

FORMATIVE YEARS

In his autobiography *My Life in Science*, Brenner writes: "There has been only one quest, the quest to find out how organisms are encoded by their genes, to study that unique property of biological systems that distinguishes them from all other complex natural systems, of containing an internal description of themselves".

His part in this quest started at a very young age. As a three-year old he experienced one of the first turning points in his life. "I stopped being a baby and I gained a determination to do something in life," remembers Brenner, who was born on 13 January 1927 in Germiston and could read by the age of five.

After skipping a few grades, a 15-year old Brenner started medical training at the University of the Witwatersrand (Wits). It wasn't necessarily that he wanted to become a doctor. He saw it as a way to become a working scientist – an aspiration he had held ever since reading *The Young Chemist* by F Sherwood Taylor as a nine-year old.

He obtained his MBChB degree in 1951, after interrupting his medical studies for three years to do basic scientific studies and to obtain an MSc degree. As a somewhat reluctant medical student he lacked the same single-minded passion for his clinical studies as he had for his part-time research work. After failing his final clinical medicine exams, Brenner had to extend his training by six months to qualify as a doctor. He never practised.

His career as an independent researcher took off in 1945 during his Honours year, when he published his first scientific paper in the *South African Journal of Medical Science*. It was about the use of fluorescence microscopy to study the effects of Pellagra, a disease caused by chronic vitamin B deficiency. It was followed by a second in the science weekly *Nature*.

In between studies Brenner was also involved in student politics as Director of Research and Study of the National Union of South African Students (NUSAS) and as President of the Wits Student Representative Council.

His name lives on at his *alma mater* through the Sydney Brenner Institute for Molecular Bioscience. Sydney Brenner Institute for Molecular Bioscience was a virtual institute approved in 2009, but formally constituted in January 2014. In the late 2000s, he also enjoyed South African ties with the Stellenbosch Institute for Advanced Study (STIAS). Among the 26 honorary degrees bestowed on this recipient of the prominent Albert Lasker Award are four from South African institutions, and among the long list of accolades also the country's National Order of Mapungubwe in Gold.

It is at Wits where Brenner's wife, May Balkind, first noticed him while he gave one lecture on basic statistics to her psychology class. They married when both were studying in the UK. Brenner was working towards his DPhil at Oxford University, thanks to a coveted Overseas Scholarship of the Royal Commission for the Exhibition of 1850, while May studied at London University. The couple, who had four children, was married for nearly 58 years before May passed away in January 2010.

MOLECULAR WORK

Yet another important turning point occurred in April 1953 when the 26-year old Brenner was working on his doctorate. Along with fellow scientists from Oxford he drove to Cambridge to view James Watson and Francis Crick's newly unveiled DNA model. Brenner spent some six hours in deep conversation with Watson about the possibilities it opened up for molecular biology, and the three subsequently struck up a lifelong working relationship.

Between 1954 and 1956, Brenner taught physiology at Wits – the only time he was employed in South Africa. For the next 35 years he worked at the Medical Research Council's Laboratory of Molecular Biology (LMB) in Cambridge, and became part of the 'renaissance of biological discovery'.

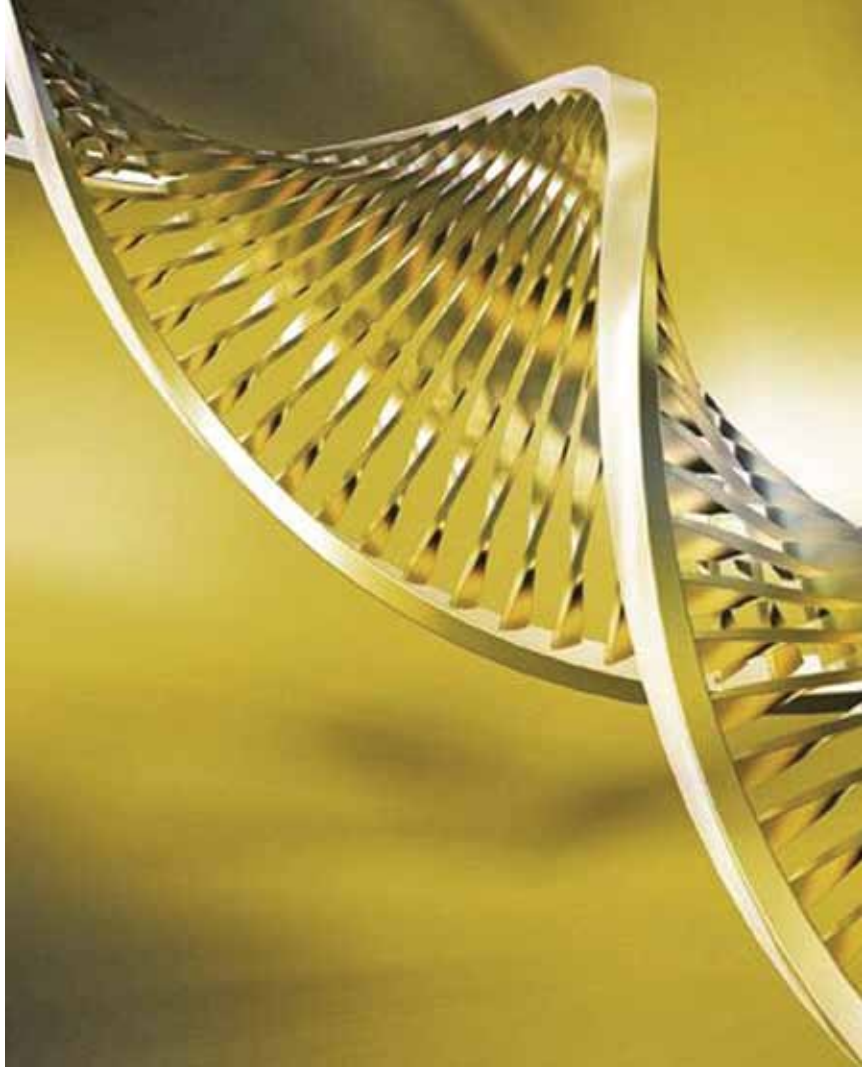
Most notably, together with Crick and others, Brenner showed that the genetic code is composed of non-overlapping triplets. Three bases, or a codon, encoded one amino acid, which is the basic building block of proteins. Together with Francois Jacob and Matthew Meselson he also proved the existence of messenger RNA (mRNA), which explains how information is transferred between DNA and proteins.

In a booklet published in Singapore in October 2015, James Watson wrote: "Genomics owes a great deal to him [Brenner] and his ideas; not just for the worm, which is what his Nobel Prize was for, but also technologies like massively parallel signature sequencing, which allowed gene expression to be analysed on a scale few could have imagined earlier".

SCIENCE COMMUNICATOR

A journalist once wrote about Brenner: "When he starts to talk you are swept along in the icy, buffeting current of ideas, shocked and exhilarated to the point of exhaustion – and still he goes on talking. Profundities, puns, anecdotes and opinions all rush and jumble together".

Brenner is indeed known for his wit, his all-consuming work ethic and his ability to keep a conversation going into the early hours of the morning. This seasoned traveller can also clearly and colourfully explain difficult scientific concepts. From 1994 to 2000, he for instance wrote monthly columns for *Current Biology*.



About the need to communicate science, he says: "I like to talk as I think we all need to keep the conversation going. And I think many things can be explained quite simply. The important point is that we are not machines performing tasks but human beings".

A MENTOR TO OTHERS

Brenner served as LMB Director between 1979 and 1986, and then until 1991 as Director of the MRC's Molecular Genetics Unit. During his Cambridge years, he enjoyed various associations with other British and American institutes, including The Salk Institute, The Scripps Research Institute and the Neurosciences Research Programme. From 1996 to 2001, he was President and Director of Science of The Molecular Sciences Institute at Berkeley.

In his later life Brenner not only took on Singapore's development, but also two other major mentoring efforts: the Okinawa Institute of Science and Technology (OIST) in Japan and Janelia Farm at the Howard Hughes Medical Institute in the US.

In his biography, Friedman sums up the differences between Brenner's various "grand mentoring efforts". "The Singapore enterprise represents an excellent example of Brenner's skill in harnessing the energy, commitment, and financial resources of a young and prosperous country eager to join the front rank of international biomedical research."

"In contrast, OIST provides an educational example of how long-standing cultural influences that are perceived to hinder cutting-edge research can be altered... The Janelia Farm experiment is designed to free outstanding young scientists from the onerous burden of writing grants in search of financial resources from funding entities not known for supporting high risk and innovative science. It is also a heroic attempt to bring scientists from multiple scientific disciplines together in the hope of achieving the sort of cross-fertilisation that is difficult, if not impossible, to achieve in more structural environments."

What has driven Brenner to take on challenge after challenge, even well after retirement age?

"I believe that we should not be judged by our prizes and medals but more by what we leave behind in the science that we have created and the people we have influenced and trained," says Brenner, who counts five Nobel Laureates among the postdoctoral students he has mentored.

"It is very difficult and often a waste of time to try to change the present as the forces of conservatism are very strong," notes Brenner. "But, as Max Planck observed, those in power are old and will retire and die. The young will inherit the future and that is why I work as much as possible with young people."