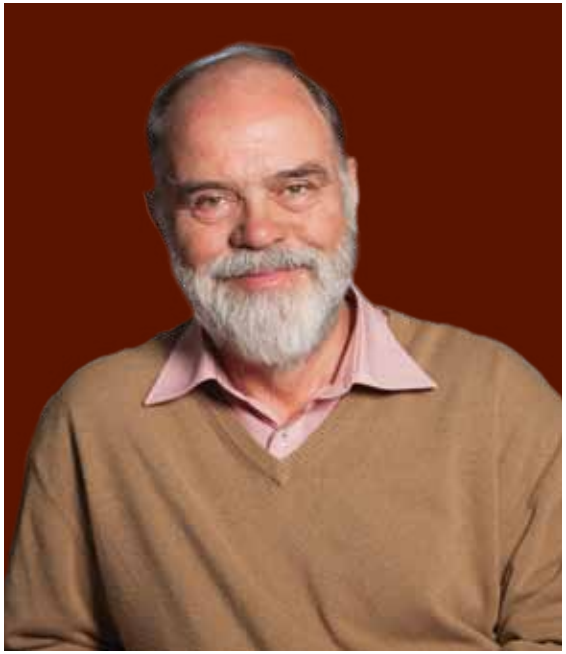
PAUL VAN HELDEN



TOP THREE AWARDS

- ASSAf Science-for-Society Gold Medal, 2009
- NSTF Award for Outstanding Contribution to Science, Engineering and Technology, 2004
- Gold Medal Award from the South African Society for Biochemistry and Molecular Biology, 2001

DEFINING MOMENT

In 2008, *Nature* published a major paper that showed that identical twins show DNA methylation differences, confirming the results of a study that I had undertaken with a Masters student, Mark Bedford, in 1988, and which had been rejected by *Nature*. Imagine my thoughts and emotions when I saw this paper! I learned a great deal from this experience. For instance, that it is very difficult to be ahead of one's time and to challenge dogma. It made me very determined to challenge dogma and stick to my findings, which I have regularly done since then in my TB career.

WHAT PEOPLE DO NOT KNOW

I am a lifetime member of the Botanical Society and an honorary ranger with South Africa's National Parks service.

CHALLENGING THE TB DOGMAS

Starting out as a basic scientist, Paul van Helden has had a great impact on changing our understanding of tuberculosis (TB) and TB treatment in South Africa.

Starting in the late 1980s, he pioneered the use of molecular technologies to study the country's tuberculosis epidemic. Today, with drug resistance a growing problem, the country's health care system routinely uses the technologies he helped pioneer to diagnose TB in the clinic.

Although a nature conservation buff, Van Helden has spent the majority of his career at Stellenbosch University's (SU) medical campus in Tygerberg. "What I've tried to do is create a research environment that ranges from the basic to the applied in TB, with a focus on making a difference," he says.

Growing up in Bergvliet, in the southern suburbs of Cape Town, Van Helden was fascinated by nature. At the age of 13 he joined the Botanical Society of South Africa. As a pre-teenager his favourite books were biographies of famous scientists like Marie and Pierre Curie. To his non-academic parents their son's deep interest in science was a bit of a mystery. Yet, they were pleased that he wanted to study for a university degree, hoping it would set him on the track to a good job.

Van Helden did not find his undergraduate studies at the University of Cape Town particularly fulfilling. He felt constrained by the course content, which at the time he thought had little apparent connection to usefulness. By the end of his first degree, he felt disillusioned with academic life. He didn't believe the course had taught him anything practical, or conferred any useful skills.

Nevertheless, he stayed on for an Honours degree, reasoning that a Bachelor's degree wasn't enough to give him an edge in the job market. As it turned out, the Honours course in biochemistry suited him far better, since it was his first chance at doing a research project. "I was far happier," he recalls. But his sights – and those of his parents – were still firmly set on getting a good job at the end of the course.

After his Honours in 1974, Van Helden was offered a job as a chemist at the City of Cape Town's sewage plant in Athlone. His parents approved, but a split-second decision on the drive home from the job interview changed things. Mindful, perhaps, of his childhood dream of becoming a scientist, he took the UCT turnoff and went to see his Professor, Claus van Holt. Van Helden asked him for advice: Should he take the job?

The Professor made a counter-offer: If Van Helden wanted to, he could have a PhD studentship in the Biochemistry Department. That way, he could see whether he liked research – and if not, there would be other jobs after his PhD. Van Helden's parents were distraught at the prospect of their son turning down a well-paying job. But his mind was made up. He would accept the offer.

EARLY ACADEMIC LIFE

For his PhD, Van Helden studied protein sequencing. This technology was established, but rare in the mid-1970s. It was very basic research, and in truth Van Helden finally found it a bit boring. But his supervisor advised him to be patient. "I remember him saying that part of doing science is having the tenacity to hang in there, to get the job done. He told me that your PhD is your passport, your certificate of training. After that you can choose what you want to do."

Van Helden received his PhD in 1978. Over the next two years he worked as a Senior Professional Officer in the Department of Medical Physiology and Biochemistry at SU's medical school and expanding on his PhD work and moving it to a new field, he worked on chromatin – a complex of DNA and proteins that forms chromosomes – in muscle cells. But the field of molecular biology was developing rapidly, and Van Helden felt that he needed to be exposed to new ways of doing things.

He left South Africa in 1981 to take up a two-year postdoctoral fellowship at the Roche Institute of Molecular Biology in New Jersey, USA. The purpose of his trip was to be exposed to different ways of running a lab and research group and to learn 'recombinant DNA technology'. At the time,

only a couple of people knew how to do it in South Africa, and they, too, had learnt it abroad.

Van Helden returned to SU in 1983, where he continued to work on muscle cell biology. But soon his interest started shifting towards DNA structure and epigenetics, the study of how different parts of the genome can be switched on or off, by DNA structural change or methylation changes. This happens naturally as our bodies develop and age, but can also be caused by external factors like our diet or environment. It plays a key role in disease like cancer.

He also pondered how the molecular biology techniques he had learnt overseas could be applied in South Africa to improve treatment outcomes for patients. A big advance in the field had happened in 1984 when California-based chemist, Kary Mullis, invented the polymerase chain reaction (PCR) technique. This is a type of 'molecular photocopying' that allows scientists to make millions of copies of DNA samples, making them far easier to study. Mullis received the Nobel Prize for it in 1993.

Today, PCR can be done in minutes using specialised equipment, but in the late 80s the technology involved a lot of hard work. Van Helden and his colleagues got into it on a manual basis, using water baths and stopwatches. It was too labour-intensive to be useful, so with the help of two technicians, Van Helden's group designed and built Africa's first automated PCR instrument out of four hair dryers. The instrument vastly enhanced his team's ability to do PCR. So he began looking for an area of research where he could apply the technology to health problems facing his country.

MOVING TO TB

His attention quickly turned to tuberculosis. The disease was a big problem in South Africa, especially in poor communities and among mineworkers. However, the way that TB was diagnosed had not kept up with advances in science.

Diagnosis was a lengthy process involving culturing bacterial cells from the spit of a patient. PCR technology could speed it up significantly. But the idea of using molecular science for such purposes was almost unheard of in a low-resource setting such as South Africa's public health system.

Van Helden and one student started applying molecular techniques to investigate how well these technologies could be applied to TB diagnosis and to gain new insights into the disease. Early successes, coupled with his appointment as Head of the Division of Molecular Biology and Human Genetics (then Medical Biochemistry) and also Director of the Medical research Council (MRC) Centre for Molecular and Cellular Biology in 1992, allowed him to devote more inputs to TB and persuade colleagues and coworkers to join his TB effort and start their own projects. International grant support followed, which by 2004, had established the team well enough to allow him, together with colleague, Professor Valerie Mizrahi, to be given a grant that established the Department of Science and Technology/National Research Foundation (DST/NRF) Centre of Excellence for Biomedical TB Research, where he is now Director.

But in those early days of TB research there was some resistance to new technology. The idea of using molecular biology to study and diagnose TB in the country was thought by many to be "too expensive and not practical", Van Helden says.

Van Helden speculates that part of the problem was that early results started to challenge long-held beliefs and dogmas dear to many. However, he and his colleagues used such techniques to great effect. For example, they found that contrary to common belief, patients turning up with TB after already having been treated and declared free from the disease once before were often re-infected with a different strain: In other words, it was not a case of relapse.

These results were published in a seminal paper in the *New England Medical Journal* in 1999. The paper kick-started a whole new field of study into TB re-infection, and changed the thinking about how to conduct and interpret drug trials in the field. His team's work in antibiotic resistance has also been instrumental in pushing for routine testing and modification of therapy.

Over the years since then, Van Helden and his colleagues have built up an impressive body of publications from the SU medical school.

He was also instrumental in giving a boost to Professor Andreas Diacon, a South African entrepreneur who runs clinical trials for TB drugs. Diacon's work has resulted in new antibiotics being trialled in conjunction with Van Helden's centre of excellence and made available for treating TB. "I'm very proud of being a part of that," he says.

In 2009, the scientific publishing company Thomson Reuters rated Paul van Helden the fourth most impactful TB research researcher in the world. "That to me was my crowning achievement," he says. He shares such accolades with his colleagues, since he believes that surrounding himself with a great team has been the key to his success. He enjoys teaching students, and regards them as his extended family. "I still feel a thrill every time one of them publishes a paper."

He has worked with and for the MRC under every single president of MRC, and at Stellenbosch under every medical dean except the first. Over his career Van Helden has received a number of awards and prizes. But most of all he treasures the memory of the surprise party thrown for him by his centre and department for his 60th birthday!

LOOKING AHEAD

When he retires he plans to continue to be involved in TB research part time, and spend the rest of his time on nature conservation. As lifetime member of the Botanical Society and an honorary ranger with South Africa's National Parks, he has to serve the parks by providing a minimum of 100 hours service every year. He currently clocks well over 400 hours per year.

His wife is also a Professor in his centre and also an honorary ranger. Together, they have worked on projects like tracking down the original 100 markers placed out in Table Mountain National Park in 1966 to mark out botanical plots. These are now being used by the South African Environmental Observation Network and students to investigate changes in vegetation and climate. He also goes to the Kruger National Park at least once a year as part of a project to study TB in wildlife – a growing concern in South Africa's wildlife reserves.

Today, molecular diagnostics is no longer in the fantasy realm of South Africa's health care system. In 2011, South Africa's health minister announced that an automated PCR machine called GeneXpert would become the first-line test for TB in the country. Although Van Helden does not want to credit himself for this change in policy, he likes to believe that his early work led to some of the changes seen recently in the way TB is addressed nationally.

There are also many more scientists working on TB today than when he started out. But TB still has far fewer people working on it than HIV – something he thinks is "disgusting" given that the former is curable. The two diseases are linked in South Africa, where immune systems weakened by HIV are more vulnerable to TB infection. Van Helden remains committed to study only TB. "If you don't understand them separately, then you will have difficulty working on two."

He is highly critical of the way medical, veterinary and biological science is hamstrung by excessive regulation and red tape. "The science environment in South Africa has changed in some ways for the worse, by creating overly strict regulation and monitoring. We are being over-governed and over-regulated, spending more time trying to comply with the rules, writing reports and chasing grants."

However, to Van Helden, who was an active scientist in South Africa during the academic boycotts of the apartheid era, the opportunities given to students today to travel and study all over the world are enviable. It also spells good news for the future. "We are now part of a global network in a way that was impossible in the first half of my career. That's enormously exciting and encouraging," he says.

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Legends of South African Science

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