I still remember very vividly the first lecture that I ever heard from Prof. Peter Beighton. This was shortly after he arrived in Cape Town in 1972. Were it not for Peter, I do not think that I would ever have entered the field of human genetics. With his enthusiasm and brilliant presentation, and the capability of evoking excitement and dreams, Peter Beighton inspired me. Shortly after I had heard that lecture, I presented myself at the Department of Human Genetics, which was newly established and the first in Africa. I asked him whether I could participate in any research projects. I was particularly drawn to his research projects, as it appeared that they opened up new possibilities for understanding biology in different populations, which might have relevance for the general population. Peter’s stories of his hiking through the Sahara Desert with the Tuareg, and his stories from different populations in Africa, inspired me and elucidated for me for the first time the power of studying rare families and their ability to inform general rules of biology.

As a medical student, I then pursued many research projects with Prof. Beighton. I recall travelling with him to the Kalahari Desert in an effort to understand and explore the basis of steatopygia in the Khoisan people. I also recall very vividly the first introduction that Peter made for me to patients with increased bone density. Peter was an expert and had already specialised in patients with bone dysplasias, including increased bone density, and had authored authoritative manuscripts on sclerosing bone dysplasias.5–7 I was fortunate to go with Peter to visit families with sclerosteosis in different parts of the country. These were very moving moments as I saw, first hand, the impact of this increased bone density on patients.5–7 In a few instances, we actually saw, to our deep sadness, the increased intracranial pressure leading to severe symptoms and occasionally also to death, as a result of the increased density of the skull. These vivid images have stayed with me throughout my life and have also inspired me to look and see what we could learn from and do for those with rare conditions.

After I moved to Vancouver, to the University of British Columbia from Harvard Medical School in 1983, and founded my first company, Xenon Genetics, I remembered those patients with sclerosteosis and went back to Peter. I persuaded him and others to send a postdoctoral fellow to the USA in an effort to bring DNA to clone that particular gene. When I looked at the X-rays of these patients with Peter, it was obvious that this was not a disorder of osteoclast overactivity, but appeared to be most likely due to unregulated overexpression of the osteoblast. I already recognised at that point that an understanding of the cause for sclerosteosis could potentially lead to a fundamental understanding of the regulation of osteoblast activity. This, in turn, could lead to the opportunity to influence osteoblast activity, with the potential to treat osteoporosis in the general population. With this particular perspective, the gene for sclerosteosis was cloned and discovered.8 The protein was termed ‘sclerostin’, and this represented the discovery of the key regulator of transcriptional activity of osteoblasts in humans. Knocking this out or deleting it, as was seen with patients with sclerosteosis, resulted in osteoblast hyperactivity and increased bone density. As a result of this, it was apparent that if one developed an antagonist to this transcriptional regulator, replicating what is seen in sclerosteosis, this would lead to upregulation of the osteoblast. This eventually led to the development of humanised monoclonal antibodies that inhibit this particular transcriptional regulator, resulting in upregulation of the osteoblast. Humanised monoclonal antibodies against this novel target are currently in phase III development (Amgen, USA), and offer hope for the development of new approaches for treatment of osteoporosis in the general population. This has also opened up a field of investigation into regulation of osteoblast function.

The particular concept that by studying a rare disorder, one could derive insights that are pertinent to the general population and general biology, and would lend therapeutic targets, was a very landmark inspiring moment for me. It continues to be a beacon to me in my approach to human genetics and the approaches to drug development for the future. Genetically validated targets still represent a most important approach to ensure success in drug development. This was also exemplified by our search for genes causing congenital insensitivity to pain. I was first aware of this condition on seeing a few kindreds of the Cape Malay community practise a unique ritual, where individuals could pierce their own body parts, including the tongue, or walk on nails, and experience no pain. I was immediately struck that if there was a way to pierce their own body parts, including the tongue, or walk on nails, and experience no pain. I was immediately struck that if there was a way to

When I finished my medical studies, I continued in an internal medicine residency at Groote Schuur Hospital (GSH). At the same time, I approached Prof. Beighton again with a view to doing a PhD
in medical genetics. At one of the first clinics I went to in early 1977, patients attended with inherited chorea, which was not deemed to be Huntington's disease (HD) as it was believed that HD did not exist in South Africa (SA). I saw the impact of this disease on families as we made home visits, and continued to identify patients with inherited chorea or HD in the population. As a result of this, when I told Prof. Beighton that I wanted to study HD, his approach was 'seems very reasonable, H is for Hayden and H is for Huntington's chorea; seems like a good plan'.

Peter's approach to mentorship was profound and inspiring. His intense enthusiastic engagement with the day-to-day activities of the scientific project was exciting. He maintained passionate involvement in all that happened and was also committed to communicating our findings to the population and to the scientific community as quickly as possible. This infectious enthusiasm, as well as his ability to give me the freedom to pursue this disease, not only in the Western Cape but also throughout every mental hospital in SA, was really an opportunity for me to express my own sense of wonder, curiosity and hope for new understanding of this devastating disease. This study itself ended up changing the view of the epidemiology of HD in Africa.1-16

Peter also supported my approach to the development of the first multiracial HD clinic in GSH in 1978. Together with Jim McGregor, the Chief of Neurology, a non-racial clinic (one of the first) was established, which was led by medical genetics but incorporated neurology, psychiatry, social work and other modalities to provide comprehensive care to patients. Peter recognised early on that the key to providing support for patients was also to take care of the caregivers and the family.11 The approach to caring was very significant as we recognised that the patient is not the only focus for care, but also the family and the patient's place within their own community. Peter also encouraged me to believe that the importance of this project was profound and central to the development of human genetics in SA. He supported the investigation of HD in Mauritius11 and other small communities within southern Africa.12-15 He also helped to raise funding from different sources, such as the Mauerberger Foundation, in an effort to allow this project to reach its particular goals. In a sense, this was all serendipity. Serendipity that, firstly, I was able to have this opportunity to work with Prof. Beighton, but also serendipity that I saw patients with HD at the first clinic that I went to, which then supported my inquiry and my pursuit of knowledge that continues to this day.

A good test of mentorship is the ability to inspire others, a sense of play and also the recognition that together we can change the landscape and bring new knowledge to the world. Peter made me think that we could change the world, even from Cape Town, and that a sense of adventure and play was a very important component and a lifelong gift that empowered us to express our fullest potential. Another example of his profound leadership was his unique approach to giving lectures. His lectures were always stimulating, exciting, inspiring and sometimes shocking. He quickly educated all of his trainees on how to give a lecture, how to focus, how to draw attention, how to bring humour, how to shock and also how to inspire. Peter gave advice as to how to tell a story and develop a narrative; this particular skill was very important for an early fledgling scientist. Peter's inspiration in this way has played a key role in my ability to improve my communication skills throughout my life. Peter always shared his slides, his books and his perspectives with me in the most generous way, and was always willing to provide critique and support, at all times of the day, nights, weekends and holidays. He taught me simple principles, such as how to create a captivating title in a talk, how to have figures that tell a story, and how to make sure that the presentation is not filled with too much data that would be best put within a manuscript. How to arrange your slides with the recognition that a picture is better than a thousand words is a principle that is still deeply embedded in me to this day.

Another exciting part of being in the Department of Human Genetics in the '70s was Peter welcoming all of his trainees to interact with visiting professors who came from all over the world. I still recall with great fondness the visits of David Smith, Alan Emery, Jurgen Spranger and others to SA in the late '70s. I remember showing David Smith a patient with a smooth philtrum and a particular facies with some epicantic folds and obvious developmental delay. This resulted in the first child in SA being identified with fetal alcohol syndrome. This presentation was later submitted and published in the SAMJ.12-15 As part of this visit, I also identified, with David Smith, the first patient with fetal hydantoin syndrome, which was quickly translated to publication in the SAMJ.15,16 The friendships that were encouraged by Peter's generosity of spirit had influence throughout my life. I visited David Smith and Arno Motluskly in Seattle and also Judith Hall, who continued to play a very important role in my career. Judith was the person who persuaded me to come to the University of British Columbia when I was doing a fellowship at Boston Children's Hospital.

Even though Peter was thrilled with and had a keen sense of enjoyment of his trainees and people around him, he also understood that for each of us to make a mark, it was most important for us to travel and to undergo additional training in different parts of the world. I had long discussions with Peter about where to go and he provided sage advice about different parts of the USA and Canada, to which I applied. I eventually chose to go to Boston Children's Hospital, with his complete blessing and support. A key feature of those years in training under the guidance and mentorship of Peter Beighton was the strong sense that my trusted advisor really believed in me, my abilities and the objectives of my study. This empowerment brought not only intellectual courage but also technical courage, as Peter also inspired us all to collaborate with others at UCT and elsewhere. These collaborations led to the first investigation of neuroendocrine abnormalities, including impaired prolactin release, in HD, published with Arthur Vinik and others in the Department of Medicine in 1977 in The Lancet.17

Peter's mentorship of my development at this important stage has allowed me to incorporate principles that have certainly improved my ability to be a mentor. I have now mentored well over 150 people, and, for me, the independent success of these trainees is a very important part of the sense of meaning and accomplishment that I carry with me at this different stage of my career. The process of understanding this, and recognising that the success of your trainees is the greatest source of professional satisfaction, really goes back to Peter and his ability to be a role model in this way. Another important attribute that Peter has was that even when the day looked bleak and the opportunities for funding looked grim, the sense of irrational optimism and a positive perspective was ever present. This, coupled with a sense of adventure, a sense of humour and the recognition of what one learns by observing nature around you, were key ingredients in our training.

The opportunity to accompany Peter on numerous trips throughout the Western Cape, the Transvaal, the Kalahari Desert and, for some, even to Tristan da Cunha, provided sources of great inspiration, and demonstration that by observing nature around you and rare populations, there was an opportunity to learn profoundly and gain deep insight that can have relevance for human biology as a whole. These principles are well recognised today, but we had already fully accepted them in the mid-'70s in the Department of Human Genetics in SA. This sense of work feeling like play, and the feeling that we did not work for a living but rather with a sense of fun and excitement in everything we did, was a key reward in that department. It was a great, wonderful adventure.

I am deeply grateful to Peter for his mentorship, and for the more than 40 years of friendship, fellowship and mutual support that has
occurred over this particular period. I wish Peter the best of health and the best of success, and also want to give a deep acknowledgement not only to Peter but to Greta, his partner for life, who provided undying support for everything we did with a sense of warmth, encouragement, generosity of spirit and also a sense of great fun and adventure.
