Out of Africa and into epigenetics: discovering reprogramming drugs

Peter Jones

The unsolicited letter from the reviewer of our manuscript submitted to the *European Journal of Cancer* arrived at the Department of Biochemistry at the University of Rhodesia in March 1972 as I was completing my PhD under the guidance of Professor Arthur Hawtrey. The University was a multiracial island in a segregated country suffering under UN sanctions and the beginnings of a civil war. My advisor Joseph Taderera, who was black, had been arrested in front of me in the lab for smuggling AK47s into the country and the future of my science career looked bleak. The letter, which is the only one I have ever received from an anonymous reviewer, was from Bill Benedict in the US, complimenting me on our work describing how DNA-synthesis inhibitors used to treat cancer could cause oncogenic transformation themselves. By breaking the wall of reviewer anonymity, he gave me the chance of a lifetime.

Going to graduate school in Rhodesia as a PhD student of the University of London gave me a different perspective on science, namely one of self reliance. There was no other University within hundreds of miles and there were only two seminars by outside speakers during my entire degree course. You had to make most things like fetal calf serum for yourself and you relied on surface mail for the scientific journals to arrive six months behind everyone else. Without hesitation, I seized this unforeseen opportunity and wrote back to Bill asking if I might come over to the US as a Postdoc. Maybe I would not, after all, be trapped in Britain's rebel colony and possibly be sent to the bush to fight against Joe Taderera and his AK47s.

My wife and I arrived in Los Angeles in 1973 with a five-month-old baby and three green cards to join Bill at Childrens Hospital, which was located on the mythical Sunset Boulevard. I continued work on chemotherapeutic drugs and this is when the scientific turning point happened without warning. We treated a mouse embryo cell line with the drugs and then kept the cells as monolayers for six weeks to see if they turned into foci of cancer cells. Maintaining cells for that extended period required twice weekly medium changes, which meant frequent contamination by moulds, yeasts and bacteria. One Monday morning, while we were changing media, a large mould seemed to be growing in a dish exposed to 5-azacytidine (5azaC), a new drug from Czechoslovakia. When I examined the presumed mould, I was amazed to see a huge syncytium of multinucleated cells visible to the naked eye. It was almost an Alexander Fleming type moment, because the 'contamination' represented a total switch of phenotype into muscle. I was elated because we seemed to have the first drug capable of completely reprogramming cells — maybe the 'philosopher's stone' of developmental biology.

After the Postdoc was over, my family and I went to Cape Town for two years and my first student Philip Constantinides was assigned to prove that the muscle phenotype was authentic. He nearly fell off his lab stool when he saw a cell twitch spontaneously. We sent the first paper to *Nature* from Cape Town in 1976 and I still recall being incredulous when the reviewer asked for further proof that a striated twitching cell was indeed muscle. Sometimes you have to believe your eyes.

We knew that 5azaC had to get into DNA to cause reprogramming, but what was the molecular mechanism? I accepted a faculty position at USC back in LA in 1977 and began work with my second student Shirley Taylor to find out. We had not the vaguest idea how it might work until I was being interviewed by Bob Stellwagen for what I thought was an unnecessary hurdle required to get a joint appointment in the Department of Biochemistry. He listened to my description of 5azaC and then coolly asked, "Have you thought of DNA methylation?" I, in my ignorance, answered, "What's that?" In four weeks we had the answer, and as a result of that question posed during a painful interview process, we showed that 5azaC was a potent inhibitor of methylation and linked DNA methylation and differentiation for the first time. Our paper in *Cell*, published just four years after we defined the phenotypes in *Nature*, provided a tool for many others to use in the quest to unravel epigenetic mechanisms. But perhaps the most satisfying thing of all is that 5azaC is now used all over the world to treat patients with myelodysplastic syndrome, and the era of epigenetic therapy has arrived.

None of these things would have happened, but for a surprise letter, a completely unexpected change in phenotype and a simple question during a job interview. Thus, while I still have Africa in my blood, coming out of Africa allowed me to participate in the great endeavour to decipher the human Epigenome and to help in making a difference in the lives of cancer patients.

Peter Jones is in the USC Norris Comprehensive Cancer Center, 1441 Eastlake Avenue, Los Angeles, CA 90033, USA.
e-mail: pjones@med.usc.edu

COMPETING FINANCIAL INTERESTS
The authors declare that they have no competing financial interests.