Perseverance when the going gets tough

M. Celeste Simon is Scientific Director of the Abramson Family Cancer Research Institute and Arthur H. Rubenstein, MBBCh Professor of Cell and Developmental Biology at the University of Pennsylvania. She studies tumour and stromal cell responses to variable oxygen and nutrient levels and is a devoted mentor of biomedical trainees.

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Pursuing a scientific career involves overcoming seemingly insurmountable setbacks. No scientist is able to avoid them and neither have I. I first became fascinated by the prospect of doing research as a high school junior attending Sister Eileen Freschette's chemistry class at Ursuline Academy, in Cincinnati, Ohio. The molecular structures and chemical equations provided a real sense of how the world worked. Chemistry changed my entire approach to academics, turning a truly mediocre high school grade point average into straight A's. I planned to major in chemistry in college and go into the pharmaceutical industry. I would be following in the footsteps of my pioneering mother who, in the 1950s, was one of few women to graduate with a chemical engineering degree from Louisiana State University in over a decade.

Unfortunately, the college level chemistry and calculus classes proved daunting, and I almost abandoned my dream of becoming a scientist (setback number one). After drifting through a few potential majors, I settled into microbiology. A lecture on tumour virology sparked the same excitement as when I first studied chemistry and motivated me to enter a graduate program in tumour biology. My project was going well, but my thesis advisor unexpectedly left the Department before I completed my PhD (setback number two). I applied to five of what I thought were the best graduate programs in the country and entered Rockefeller University in New York. Leaving my comfortable mid-west existence for Manhattan involved a great deal of courage and significant culture shock, but I took the plunge!

In the labs of William Hayward and Hidesaboro Hanafusa I built on the findings of Bill, Susan Astrin, and Ben Neel, demonstrating that avian retroviral DNA can insert into genomes at specific loci to transform normal cells into malignant ones. I had what I thought was a brilliant hypothesis: whereas certain viruses co-opted c-Myc to induce B cell lymphoma, others generated distinct tumours by inserting into different, yet to be defined, oncogenes. I would use the retroviruses to discover oncogenes for neoplasms that had no defined genetic basis. Setback number three

quickly ensued: the retrovirus I was studying caused tumours by a different mechanism and I was unable to use it to identify new cancer-causing genes. Previous students in the lab had become renowned scientists, and I feared I would not even survive my PhD. However, in my fifth year everything came together and I earned my degree.

A brief postdoc with Joseph Nevins was cut short when he left for Duke University. I did not feel ready for a faculty position, and looked for postdoc positions with my husband Brian Keith, who was also on the job market. He joined Gerry Fink's lab at the Whitehead Institute of the Massachusetts Institute of Technology, while I entered Stuart Orkin's group at Boston Children's Hospital, Harvard Medical School. What could have been setback number four, became a great opportunity.

I began working in the relatively new area of homologous-recombination-based gene targeting in mouse embryonic stem cells (ESCs) to generate mice lacking specific alleles. Gordon Keller had previously established how to turn pluripotent ESCs into embryoid bodies that develop hematopoietic lineages. I began trying to differentiate ESCs that were wild type or mutant for the red-cell regulator *Gata-1*, aiming to generate hemoglobinized red blood cells in wild-type cultures and demonstrate that they failed to develop in mutants. Months of failure ensued. I became so frustrated that I told my husband I was done with science, and might look for work in a bakery, or perhaps become a barmaid! He suggested an 'emergency' vacation. During a week at Squam Lake in New Hampshire, I was able to put it all aside and enjoy the gorgeous countryside. I returned to the lab to be greeted by Stu's huge smile. The last-ditch experiment I set up before my vacation had worked — the wild-type embryoid bodies were surrounded by brilliantly glowing red cell clusters, and the mutants had none. It was a fabulous result, and the following year I published that in vitro ESC differentiation recapitulated in vivo mouse phenotypes observed in *Gata-1*-deficient mice. I now felt brave enough to go on the academic job market.

Brian and I landed assistant professorships at the University of Chicago, where I continued to work on mouse hematopoietic development using ESCs. I also began studying hypoxic responses and hematopoietic and angiogenic co-development in mammalian embryos. This seemed to impress the reviewing committee of the first ever Howard Hughes Medical Institute (HHMI) Investigator Competition in 1994, and I became an assistant investigator of the HHMI. I moved to the University of Pennsylvania in 1999, where I am studying tumours once again.

I recently returned to Squam Lake, roughly 26 years after that first fateful trip. So much has changed for me since I was tempted to leave science in 1990, in part because of that wonderful destination. We all suffer setbacks, and I seriously considered quitting research many times prior to becoming a faculty member. However, perseverance paid off and I have been actively engaged in science for over 40 years. The moral of this story is: never give up. Or at least take a nice holiday and think it over carefully before you do! ❐

M. Celeste Simon[1,2]

[1]Abramson Family Cancer Research Institute, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA. [2]Department of Cell and Developmental Biology, University of Pennsylvania, Philadelphia, PA, USA.
e-mail: celeste2@pennmedicine.upenn.edu

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