A tribute to somatic cell reprogrammers

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For many biologists, the ‘holy grail’ has been to derive pluripotent cells that have the potential to differentiate into all cell types of the body. They represent enormous scientific value as they can be used to study differentiation, the onset of disease and, in the long term, offer a significant therapeutic potential (Colman and Dreesen, 2009). Long before Martin Evans derived the first mouse embryonic stem cells (Evans and Kaufman, 1981), which are considered to be the ‘gold standard’ of pluripotency, scientists were already developing processes to convert somatic cells, which are derived from adult tissues, into the early, pre-gastrulation cells of an embryo that, like embryonic stem cells, can give rise to all cell types of the body. The ability to convert cells in such a manner has significant implications for human health, understanding development and ageing, and providing therapeutic approaches to rejuvenate damaged or injured tissue. Whilst many investigators have sought to derive reprogrammed cells using a number of approaches, there have been three key events that have exerted a profound influence on this field.

The first of these was the work of Professor Sir John Gurdon who had the ingenuity in 1958 to predict that the egg possesses powerful factors that regulate the way genes are expressed during very early development (Gurdon et al., 1958). Specifically, Gurdon took somatic nuclei from frog cells and introduced these into enucleated eggs to generate a live offspring. The ability to generate an offspring using this approach revolutionized our thinking about how a fully matured cell could be reprogrammed to an embryonic state. This major breakthrough laid the seeds of foundation for years of investigative work that attempted to generate mammalian clones using a similar approach. However, this work, although marginalized for a very long time in terms of its impact, opened up the field of epigenetics and how gene expression is regulated during development. Now, we apply this knowledge to understand how early developmental events can prime the individual for the onset of specific diseases later in life.

Indeed, it took 39 years for the second major event to provide us with a measurable understanding of the power of reprogramming. In this instance, Keith Campbell and Ian Wilmut successfully took mammary gland cells from the breast tissue of a sheep and transferred these into enucleated sheep eggs to generate the first mammalian clone—‘Dolly the sheep’ (Wilmut et al., 1997). The work of Campbell and Wilmut was a major leap forward for the reprogramming of mature adult cells, as many sceptics believed that this was an unachievable outcome. Although there was intense competition to derive the first mammalian clone, it was the foresight of Keith Campbell who realized that the cell cycle of a somatic cell would need to be synchronized to a quiescent state to achieve successful preimplantation and subsequent development to term (Campbell et al., 1996). One might argue that this was simply a transfer of technology developed in an amphibian system to that of a mammalian system, however, the 39 years of endeavour of mammalian cloners to achieve this outcome shows that this was indeed an in-depth scientific struggle. We know from other experimental models that applications or modifications that have been introduced in the fruitfly or the earthworm have a significantly higher degree of difficulty when translated into the mammalian system. However, of importance is that the work of Campbell and Wilmut not only opened somatic cell nuclear transfer work to the mammalian system, but it also provided biomedical models to study disease. It also, like the work of Gurdon, again revolutionized the field of epigenetics, and enabled us to investigate whether it was possible to produce human proteins in a mammalian system that could be secreted or purified for therapeutic benefits. Indeed, the subsequent work of Campbell and Wilmut demonstrated that, for example, an anti-coagulant factor could be generated in sheep milk through the process of somatic cell nuclear transfer where the donor cell was genetically modified (Schnieke et al., 1997). Cloning is now widely used in the livestock industry both for biomedical science purposes and to enhance the genetic traits of livestock to improve food quality.

Not only did the work of Gurdon, Campbell and Wilmut have a significant impact on the way we undertake biomedical science research today, the major ethical and moral issues associated with the generation of offspring through cloning were hotly debated. It meant changes to legislation in many countries to prevent the generation of humans through such approaches and forced legislative assemblies to consider how far cloning might be permissible; for example, whether human cells could be transferred into animal eggs to generate embryonic stem cells. Most interestingly, ethicists and social scientists were attending the same academic meetings as scientists to discuss the implications of such work. There was also the ugly fraud perpetrated by Hwang Woo Suk, who falsely claimed that he had generated
cloned human embryonic stem cells and thereby seriously tainted the field.

Whilst mammalian cloning had failed to generate any human stem cell lines for either therapeutic purposes or for the study of disease, it had two key impacts. Firstly, it reinvigorated attention on the work of Martin Evans in generating embryonic stem cells, for which he received a share of the 2007 Nobel Prize. Secondly, it laid the foundations for the next major invention. Shinya Yamanaka took somatic cells and reprogrammed them to an embryonic stem cell-like state using factors present in the egg but introduced into the somatic cells by viral delivery approaches (Takahashi and Yamanaka, 2006).

The key advance here was the generation of pluripotent cells in a non-egg environment. This in itself has created a new revolution within our field whereby scientists throughout the world are now taking somatic cells and inducing them to pluripotency using cells from patients with specific genetic or multifactorial type diseases to generate pluripotent stem cell lines. We can now ‘study these diseases in a dish’ to understand how and when the disease is first likely to trigger its phenotypic onset, affect different cell types during development and perhaps find therapeutic targets to prevent the severe phenotypic onset of these diseases.

It is most appropriate that John Gurdon and Shinya Yamanaka have been awarded the Nobel Prize this year for Physiology and Medicine. This award involved two investigators whose highly significant contributions have a two generations gap between them. However, the work of Campbell and Wilmut has clearly linked the endeavours of the two prize winners. Whilst we should be joyous in celebrating the role that each of these investigators has played in enhancing developmental biology and the potential to develop models of diseases, it is with great sadness that we should also remember that Keith Campbell passed away recently. His was a talent that was partially rewarded with the Shaw Prize in Life Science and Medicine in 2008, otherwise known as the ‘Asian Nobel Prize’, along with Wilmut and Yamanaka. Sadly, due to his death, his work can no longer be a contender for a Noble Prize. Nevertheless, his legacy will not be forgotten, as it was truly a magnificent feat that has changed our way of doing science, which has already led to significant advances for mankind just as has the work of John Gurdon and Shinya Yamanaka.

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**References**


