The 'ultimate' stem cell

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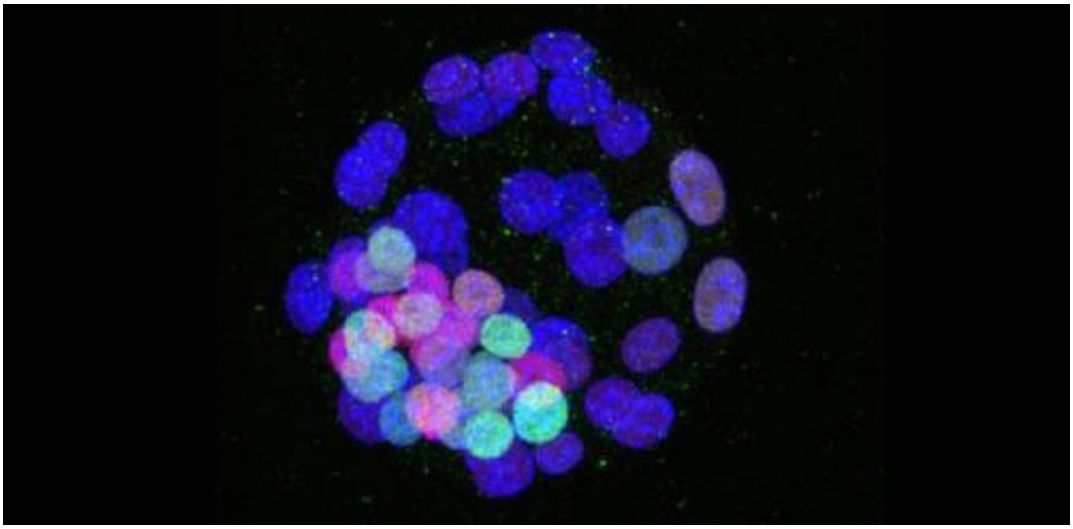

Mouse blastocyst at the pluripotent stage, when cells have the capacity to generate all of the cell types of the adult. Credit: Jenny Nichols

In the earliest moments of a mammal's life, the developing ball of cells formed shortly after fertilisation 'does as mother says' – it follows a course that has been pre-programmed in the egg by the mother. Extraordinary as this is, what happens then is even more remarkable.

Just before implantation in the uterus, the ball of cells, called a blastocyst, gains the capacity to generate all of the cell types of the subsequent adult – a feature called pluripotency. It is at this moment when everything is possible, when the history of the previous generation has been wiped clean and when the embryo begins its unique course of

development.

But, although these 'naive' stem cells have been isolated in mice – and mouse cells at a later stage of development can be manipulated to take them back to full naivety – the same has not been convincingly accomplished for humans.

In fact, in an assessment earlier this year, Cambridge researchers Professor Roger Pedersen and PhD student Victoria Mascetti concluded that the existence of naive human stem cells required confirmation by other stem cell research groups: "Like Higgs' Boson to the field of particle physics," they explained, naivety in human stem cells "was predicted from considerations of symmetry and conservation, [but] we are yet to unlock its potential."

Now researchers led by the Wellcome Trust-Medical Research Council Cambridge Stem Cell Institute have managed to induce a ground state by rewiring the genetic circuitry in human embryonic stem (ES) cells and in adult cells that have been induced into a pluripotent state. Their 'reset cells' share many of the characteristics of authentic naive ES cells isolated from mice, suggesting that they represent the earliest stage of development.

"Capturing ES cells is like stopping the developmental clock at the precise moment before they begin to turn into distinct cells and tissues," explained Professor Austin Smith, Director of the Institute, who co-authored a recent paper on the research. "Scientists have perfected a reliable way of doing this with mouse cells, but human cells have proved more difficult to arrest. They show subtle differences between the individual cells. It's as if the developmental clock has not stopped at the same time and some cells are a few minutes ahead of the others."

He added: "Truly naive human ES cell lines would not only help answer

fundamental questions about how we are made, and be useful for drug screening and tissue therapy, but they would also provide a benchmark against which other types of stem cells could be measured in terms of their effectiveness in stem cell therapy and regenerative medicine."

Over the past 20 years, research groups led by Smith and Dr Jenny Nichols at the Institute have made a major contribution both to understanding the early stages of mouse development and to determining how to make stable mouse stem cell lines more efficiently. They know enough to realise that it's very different in humans, as Nichols explained: "Pluripotent cells that seem very similar to the mouse naive pluripotent cells appear in the human blastocyst before implantation but we don't know what happens to those cells for the following week of development. We can only make assumptions based on what happens in the mouse."

Their recent study, published in September 2014 in the journal *Cell*, proves that they are closer to capturing naive pluripotency in humans: "We know almost all we need to know about the molecular requirements for creating the ground state in mice," Smith said. "We have identified the genes and growth factors involved and, thanks to a collaboration with Microsoft Research, we can now computationally model the control circuitry in mouse cells. It's reinforced our view that we understand enough to know what to look for in humans and which combinations of genes to focus on. It's now only a matter of time."

And when that happens, work will begin on comparing them with other sources of stem cells, through collaborations such as the PluriMes project that Smith coordinates, a newly launched consortium of 10 European partners focused on directing pluripotent stem cells to become bone and muscle, and a collaboration with orthopaedic surgeon Professor Andrew McCaskie (see panel).

Could naive human ES cells be the stem cell of choice for tissue therapy? "We don't yet know," said Smith. "These cells would offer the hope of having a broader and more consistent ability to differentiate into a range of cell types because they are at an earlier stage of development. But it's also entirely possible that current stem cells are good enough for some applications. The point is, we needed these new stem cells in order to find out what is best."

Lengthening the journey to joint replacement

Translating scientific discoveries to the clinic can be a major challenge, which is why Austin Smith and orthopaedic surgeon Andrew McCaskie are working together on research that could radically change the way we treat conditions like osteoarthritis.

"Osteoarthritis is a rapidly growing health problem, with over 8 million people affected in the UK," explained Professor Andrew McCaskie from the Department of Surgery. "The conventional approach is to treat the condition when the joint is extensively damaged by using a joint replacement. We want to treat the condition at an earlier stage using repair and regenerative techniques to prolong the use of the patient's own joint and therefore defer joint replacement."

McCaskie is Director of the Arthritis Research UK Tissue Engineering Centre, a national multicentre collaboration focused on both cell and cell-free approaches to regenerative therapies in osteoarthritis. He also leads another multicentre consortium (Smart Step) that aims to explore ways to stimulate the patient's own repair mechanisms by targeting their cell populations. Smart Step is funded through the UK Regenerative Medicine Platform by the Biotechnology and Biological Sciences Research Council, Engineering and Physical Sciences Research Council and Medical Research Council.

"A pivotal part of responsible translation to the patient is a clear understanding of relevant adult cell populations," he added. "Austin's expertise in fundamental stem cell biology will allow new insights into how these cells work, which may then influence their use in safe and evidence-based therapy."

McCaskie is also developing musculoskeletal science in Cambridge in a more general way: "The musculoskeletal system is uniquely reliant on linking biological form to mechanical function. We have started a networking process to develop Cambridge Musculoskeletal Science and facilitate interaction between physical and biological sciences, technology and clinical medicine, to enhance bench to bedside interdisciplinary research, with the ultimate aim of transforming patient care."

Provided by University of Cambridge