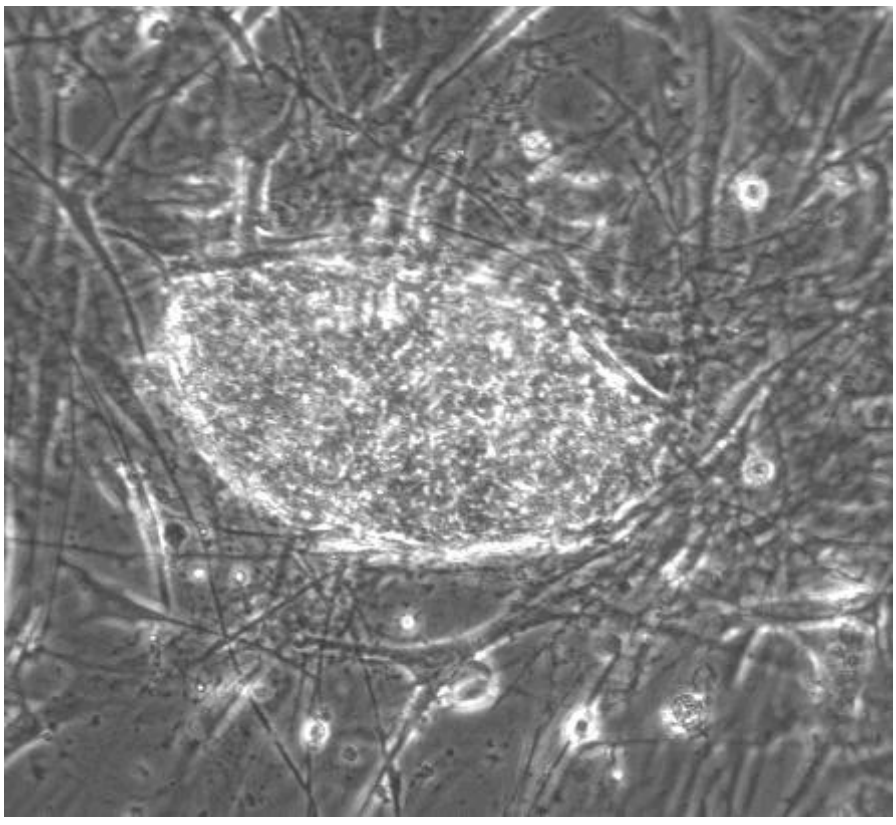
More efficient ways to erase cell memory

Can skin cells become kidney, heart or liver cells? Around five years ago, for the first time ever regeneration biologists successfully turned back fully differentiated body tissue into pluripotent stem cells using a specific mixture of transcription factors. However, the idea that it may one day become possible to create organ tissue is still a distant dream. The quantity of stem cells that can be obtained with current methods is still far too low. Dr. Maria Manukyan from the Centre for Biological Signalling Studies (BIOSS) in Freiburg is trying to find a more efficient and safer method to turn back body tissue into pluripotent stem cells.



Petri dish with a colony of human embryonic stem cells.

Once differentiated, the majority of our cells do not change their function. In contrast to stem cells, which can differentiate into many different cell types, neurons, skin cells and liver cells carry out one and the same function throughout a person's lifetime. The fact that these cells lack the necessary flexibility to differentiate into other cell types is because specific regions of their DNA are blocked by

protein components of chromatin. Genes that are not involved in the functions of a fully differentiated somatic cell can no longer be transcribed. The chief protein components of chromatin are histones, which act as spools around which the DNA winds (nucleosomes), thereby forming what is known as chromatin. This results in a so-called epigenetic code, a system above the genetic code of a single cell, which determines which genes are transcribed and which are not. When a cell divides, this code, in other words the role of the original cell, is passed on to the daughter cells.

In 2006, scientists succeeded in turning skin cells back into stem cell-like induced pluripotent cells (iPS cells) by adding just four molecules. The researchers were thus able to erase the cells' memory. Does this open up strategies to grow organs from somatic cells? Not quite. "At present, we can only reprogramme about 0.1 per cent of the cells," said Dr. Maria Manukyan, who is an independent researcher at the Centre for Biological Signalling Studies (BIOSS) in Freiburg.

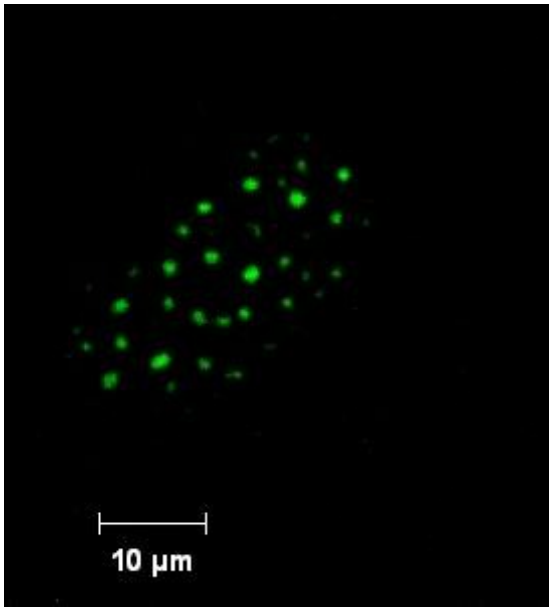
Looking for a gold standard to classify iPS cells

Dr. Maria Manukyan

Manukyan has been working on a high-risk project since September 2010. She is seeking to find a way to increase the quantity of reprogrammed human cells. The project is high risk because the researcher is not part of a huge team, in contrast to many global players working in the field of human stem cell research. She is one of four young researchers with laboratories in the so-called BIOSS Incubator. This new laboratory format enables junior researchers to work independently on their own, smaller projects whilst benefitting from the know-how of other BIOSS researchers.

Can Manukyan keep up with large research groups in the USA or other countries? There is a good chance that she can because her immediate objectives are relatively modest: rather than seeking to turn as many somatic cells as possible into iPS cells, she is hoping to find a reliable tool to help her identify and classify iPS cells. This is necessary because when researchers expose somatic cells in the Petri dish to different substances in order to return them to their original state, a broad range of different cells usually develops. Some of these cells have many true stem cell properties, whilst others have fewer.

"If we do not know whether and when the reprogramming of the cells is 100% complete, we are unable to develop a reliable reprogramming procedure," said Manukyan highlighting the problem in hand. "I am initially going to prepare a list of iPS properties, which may well become the future gold standard for classifying iPS cells," said Manukyan. The key is the cells' epigenetic code. How does the chromatin state of a stem cell differ from that of a somatic cell? Which areas are blocked by chromatin proteins and which are "open", and hence accessible to transcription proteins? What is the dynamic profile of the epigenetic code of a stem cell? In order to find answers to these questions,



Nuclei in which the non-histone chromatin protein HP1 has been stained. The protein blocks DNA and prevents the expression of certain genes.

Manukyan has imported human embryonic stem cells from the USA to investigate their epigenetic profile using molecular biology methods and to compare the stem cell profile with that of other cell types.

Medical application is a long way off

The project is only just beginning. The bureaucratic work involved in applying for and being granted permission to import human stem cells into Germany took many months. In addition, laboratory work with stem cells is not so easy as the work with fully differentiated cells. This is because "stem cells are like children". "The culture medium needs to be changed every day, and we need to closely monitor the cells as they might spontaneously differentiate into somatic cells."

Once Manukyan has defined the epigenetic profile of a human stem cell, she will be able to focus on her next goal. How can the organisation of chromatin and the activities of chromatin proteins be manipulated? Does precise knowledge of the epigenetic code help to imprint somatic cells with the stem cell code through molecular manipulations.

Manukyan also needs to find comprehensive solutions to practical problems before the technology can at some stage be made available for medical application. At present, the iPS programmers have treated their cells with rather harsh methods, for example by introducing the required molecule mixture into the cells using viruses. However, in order to be able to use the reprogrammed tissue for human applications, the researchers will have to refrain from using viruses, as this is associated with side effects that cannot be controlled. "All in all, there is great potential for medical application," said Manukyan, going on to add "but it is all about quality and quantity. It will be a long time before the medical application of iPS comes within our reach."

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Article

30-Apr-2011
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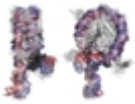
BioRegion Freiburg

The article is part of the following dossiers



Epigenetics – heritable traits without changing the DNA sequence

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