Understanding Stem Cells The Conference

4 Genetics

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In this module, the students develop the basics of genetics and epigenetics. As participants in a scientific conference, they prepare an opening, an introduction and a PowerPoint slide.

The three tasks are performed in three groups from the beginning.

90 minutes

Tasks:
Chair, introduction, PowerPoint-slide

Material:
Chair
Introduction A
Introduction B
PowerPoint slide A
PowerPoint slide B

Introduction

"The idea that genes turn us into puppets and predetermine everything is nothing but superstition."
Craig Venter, biochemist, born 1946

Split the *Chair*, *Introduction* and *PowerPoint Slide* tasks between three small groups. All groups begin to prepare simultaneously.

Chair

Two students deal with the conference day opening – similar to the conference chair. They briefly introduce the concept of epigenetics. For this they will receive an article and key questions on the topic.

35 minutes preparation
10 minutes presentation

Small group of two students
Chair exercise sheet
Chair material sheets

Introduction

Two students perform the task of introducing one researcher. They each receive material (Introduction A and B) and research notes.

35 minutes preparation
2 x 5 minutes presentation

2 small groups of 2 students
Introduction exercise sheet
Introduction A material sheets
Introduction B material sheets

PowerPoint Slide

Two groups each work on an informative PowerPoint slide. The slide should briefly summarize both topics. The basic rules of good presentations apply:

- 3–6 points on the slide or in a diagram
- clear heading (44 pt.)
- font size at least 28 pt.

Students may use PowerPoint or sketch their slide on paper.

35 minutes preparation
2 x 10 minutes presentation
2 x 5 minutes questions

2 small groups
PowerPoint-slide exercise sheet
PowerPoint-slide material sheet A
PowerPoint-slide material sheet B

If needed:
computer with PowerPoint

Following their joint preparation time, the groups present their results one after the other and thus reenact the conference day:

1) Opening by the Chair
2) Introduction of a female and a male scientist
3) Two short presentations with PowerPoint slide

Outlook

At the end of the lesson series you can take over the farewell to the conference participants: “Many thanks for the numerous interesting contributions to our conference!”
Afterwards, you can summarize your impressions on the lesson series.

Welcome Address

At conferences, the Chair takes over the words of welcome and generally introduces the topic of the conference day. The Chair is basically the chairperson of the conference.

TASK As Chair, prepare a short introduction to epigenetics:
- Delineate the term genetics.
- Describe how epigenetic changes in the genome are manifested.
- Use one of the following examples to illustrate how epigenetic differences can make an impact:
    - o Bees: worker and queen
    - o Identical twins

BONUS Lead a discussion on how the judge should decide on Bob's application.

Introduction

Important speakers at conferences are introduced. Their person and research are briefly discussed.

TASK Prepare two introductions for:
- Conrad Hal Waddington
- Emmanuelle Charpentier

OBJECTIVE **The best-known research results of the scientists should be summarized in your introduction.**

TIP Use the search terms on the Internet search material sheets to find out more about Waddington and Charpentier's research.

PowerPoint Slide

At conferences, scientists often present their results using PowerPoint slides. These present the most important facts and figures, for example using diagrams.

TASK Prepare an informative PowerPoint slide using bullet points. To do this, you will be given a newspaper article or a diagram.

PowerPoint topics:
PowerPoint slide A: Current status of cloning
PowerPoint slide B: The CRISPR/Cas9 method

TIP Read more on the topics:
Therapeutic cloning:
https://www.eurostemcell.org/what-cloning-and-what-does-it-have-do-stem-cell-research

Targeted genetic modification of iPS cells:
https://www.eurostemcell.org/crispr-changing-gene-editing-landscape
https://zellux.net (in German)

The Second Heredity

By Sascha Karberg

It is a custody case like many before and many to come. And yet, it may write legal history: The single mother of a teenager called Tom has died, and the biological father Toni is to be given custody, even though he does not even know Tom. Bob, Tom's mother's partner, who has cared for the boy like a father since he was born, is contesting this - with an unusual argument: That he is at least as much Tom's biological father as Tom's progenitor. Because what he gave the boy to eat over all the years, what he taught him and experienced with him, has defined Tom at least as much as the genes he inherited from his progenitor, Toni, during conception. The judge is confused, but Bob has already begun to explain what he means.

First, Bob holds up an image of three fruit flies, *Drosophila melanogaster*, one of the classic model organisms that have helped biologists to research the laws of heredity for over one hundred years. One of the three flies has normal, bright-red eyes. The compound eyes of the second, on the other hand, are a colourless white - the result of a mutation in a gene that determines eye colour. The third fly, in contrast, has red and white mottled eyes; some facets of the compound eyes are white, others are red. For decades, researchers could not explain this phenomenon, as the gene determining eye colour in the flies with mottled eyes is as intact as in the red-eyed fly. The only difference is that it is in a different position in the genome, which is why geneticists called the phenomenon "Position Effect Variegation" (PEV). Since then, it has been discovered that the gene is transposed to a region of the genome where genes are "packed". In other words, the DNA strands are tied up like a ball of wool. This means that the proteins that read the genetic information of a gene can no longer access the DNA; the gene remains "silent" and, as a result, the facets of the fly's compound eye remain white. In other facet cells, the eye colour gene is - by chance - a little less tightly tied up, so that is can still be read, making the facets red. This is how the red and white mottled compound eyes come to be.

Genes do not work like computers

"Yes, but what does that have to do with our case?" the judge interjects. "Depending on what the researchers feed the larvae of the PEV fly, the proportion of red and white facets in the eyes of the hatched flies varies," explains Bob. This means that genetic information is not just stoically read like a computer programme as an organism develops, but that the cells react to environmental influences - for example, the composition of the feed. The genes are packed to a greater or lesser extent and are therefore read to a greater or lesser extent. This essentially applies to all genes. But in the case of the eye colour of the PEV fly, this can easily be identified - from the eyes. "In this case, it means that not only the direct genetic ancestors determine the appearance of fly, but also environmental influences for which unrelated persons, in this case the researchers, are responsible," says Bob, who is now holding up

a picture of two bees - a queen and a worker. "This example here shows that: It is not just genetic make-up that makes us what we are."

Queen thanks to an enzyme

The difference between queen bees, who are particularly large and can lay eggs, and workers, who are barren, is a prime example of the huge influence diet can have on genes. Because as different as the queen and the workers are, their genotype is identical! A queen only hatches if a bee larva is fed "royal jelly", a secretion from special glands of the workers. In addition to water, sugar and amino acids, royal jelly contains a substance which inhibits a particular enzyme in the cells of the bee larvae. When the biologist Ryszard Maleshka of the Australian National University in Canberra blocked the production of this Dnmt3 enzyme in bee larvae, they developed into queens - without any royal jelly at all.

Genes in slumber like Sleeping Beauty

"That might be the case for flies and bees, but humans?" the judge interjects. "Even mammals such as humans have this Dnmt3 enzyme," Bob responds. It regulates the activation or deactivation of genes by sticking chemical attachments like thorns, called methyl groups, to the DNA. To a certain extent, it distributes thorns in the genome, so genes that have these "methyl thorns" fall into a kind of slumber like Sleeping Beauty and are switched off. The amount and pattern of these methyl thorns changes depending on lifestyle. Dozens of enzymes and proteins have now been identified that all ultimately influence the packing and thus the level of activity of genes. Epigenetics (Greek epi = on, at) is the branch of research within genetics that tries to explain what happens "on" or to the genes without altering the DNA blocks themselves.

Nutrition and epimutations

The effects of such epigenetic differences in humans is difficult to explore. In experiments with mice, the relationship between nutrition and gene marking can be proven by the coat colour. However, the researchers have also discovered others consequences: with a modified diet, the animals also developed certain types of cancer, diabetes and obesity far more frequently than normally. Because if methyl thorns are falsely attached to genes that counteract cancer or diabetes, then these genes are switched off - and the likelihood of these diseases increases. Therefore, some researchers no longer speak only of differences in the methylation patterns but even of "epimutations".

And these can also be researched in humans: Simone Wahl of the Department of Molecular Epidemiology at the Helmholtz Centre in Munich found epigenetic changes in blood samples from 10,000 men and women where the test person had a particularly high body mass index (BMI), i.e. if they were obese. In particular, genes that regulate fat metabolism and inflammation developed epimutations due to poor nutrition - which increased the probability of diseases such as diabetes.

"In other words, If I had allowed Tom to eat French fries and curried sausage all of the time, he would probably have developed disease-inducing epimutations," says Bob.

The same genetic material, different epigenetic patterns

However, such studies cannot completely rule out the possibility that the epigenetic differences are a result of the different gene variants of the non-related subjects. Because of this, Manel Esteller from the Spanish National Cancer Research Centre in Madrid is examining identical twins. Their genetic heritage is, by its very nature, virtually identical.

The younger the twins are and the longer they live together, the more similar their epigenetics, i.e. the epigenetic marking pattern and thus the activity level of their genes. However, if they had been separated at an early age or developed different eating habits, Esteller found significant differences in the epigenetic patterns.

Hereditary; Altered methylation signals

"This is all well and good, but it does not make Tom your biological son," the judge interjects. "After all, he got his genes from his mother and his biological father and he will only pass those on to his children, not the so-called epimutations caused by his upbringing and nutrition." "No, in addition to the genes from his biological parents, Tom will probably pass on epimutations he develops during the course of his life," says Bob, handing the judge the results of research by Michael Skinner. The biologist from Washington State University treated rats with insecticides and fungicides, so that their fertility was significantly reduced. This "environmental" damage was hereditary, because the untreated descendents of the rats were less fertile - at least into the fourth generation of offspring. When Skinner looked for the cause, he found abnormal methylation signals in two fertility-relevant genes.

Influences across generations

Of course, such experiments are not done on humans. However, there are also indications of the hereditability of environmental influences in humans: A Dutch study examined pregnant women and their children, who were starving for a long period of time in Amsterdam in 1944 because of the German occupation during World War II. Not only did they give birth to children with significantly lower birth weights, their children and grandchildren also seemed to be particularly susceptible to diabetes, obesity, cancer and cardiovascular disease in later life.

Biological and epigenetic paternity

"Allow me to summarise," says Bob to the judge. "I spent fifteen years eating with Tom, teaching him to speak and to run, rules, ideas and behaviours, trying to encourage his self-confidence and take away his fears. All of this has, if you like, left epimutations in his genome, which define his personality and will perhaps even be passed on to his children and grandchildren. In the same way as the gene variants - the specific composition of the genetic building blocks Tom inherited from his biological father Toni - will be passed on to Tom's children and grandchildren. I am therefore as much Tom's biological father as Toni and want to remain so in the future."

Difficult decision

What the judge will decide remains open. There has never been such a custody case, and not all of the experts have been heard yet, because epigenetic research is still in its infancy and many questions have yet to be answered. For example, how are environmental epimutations represented in nerve cells or fat tissue in the sperm and ova, so that the genes are similarly active or inactive in the nerve and fat cells of the next generation? However, it is likely that, in the future, judges and society will no longer only consider genetics but also epigenetics when it comes to questions of heredity.

Conrad Hal Waddington

Wikipedia writes:

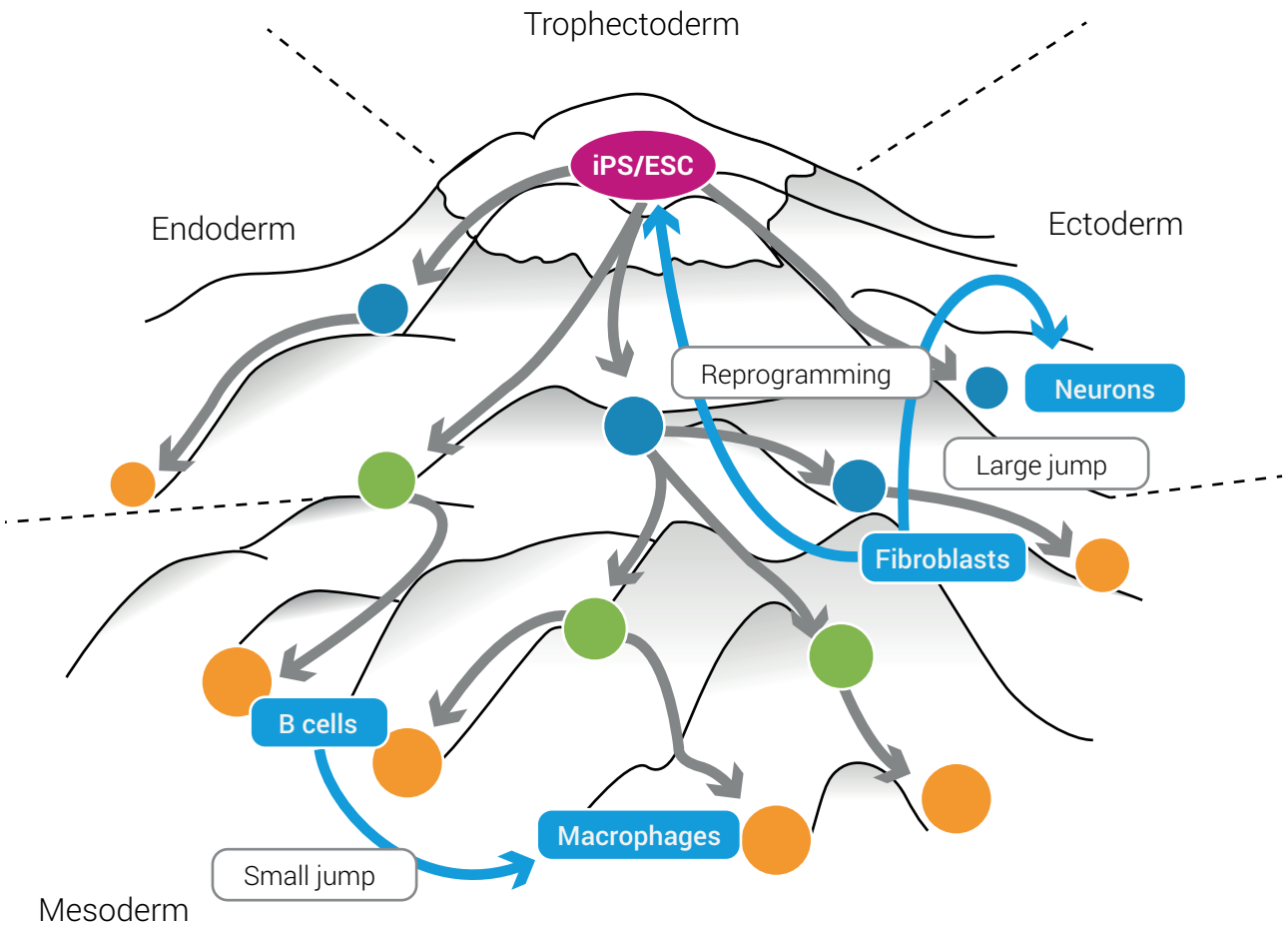
"...British developmental biologist, paleontologist, geneticist, embryologist and philosopher. He carried out basic work on developmental biology and epigenetics. Waddington is regarded as an important forerunner of today's evolutionary developmental biology (EvoDevo)" (evolution and development).

Search terms
Epigenetic landscape, channeling, buffering and genetic assimilation, EvoDevo research

born Nov. 8..1905	Eversham, England
1926	Graduated in geology at Sidney Sussex College Cambridge
From 1926	Studied philosophy, modern art and Morris dancing; studied Hans Spemann's research on amphibious embryos
1930	Specialized in embryology
1935	Cambridge ScD (Doctor of Science)
1936	Fellow of Christ's College Cambridge
1936	Albert Brachet Prize in embryology
1947	Professor and head of the Institute for Animal Genetics at the University of Edinburgh
1957	Published the essay on *The Strategy of the Genes*
† 26.09.1975	Edinburgh, Scotland

Epigenetic landscape

Waddington's original definition of epigenesis referred to changes during cell differentiation and the way in which the ability of cells to transform becomes limited with time. He was particularly interested in the stabilization of stages during the development process. To illustrate these processes, he used the metaphor of the epigenetic landscape and presented it in a model: The cell – represented by a ball – rolls through valleys of a hilly landscape and strives to reach the point of minimal energy expenditure. Waddington described how these developmental paths are influenced by genes but are also characterized by environmental factors. Because of the valley walls between the individual paths, the course cannot be easily changed. However, induction from outside can be strong enough to overcome a valley flank in the epigenetic landscape (large jump). The ball then enters an adjacent valley, development is channeled differently. The concept remains valid until today, even though epigenetics has changed its definition and today refers to various regulatory options that can influence the activity of genes independently of the DNA sequence.



Emmanuelle Charpentier

Director at the Max Planck Institute for Infection Biology Berlin, honorary professor at the Institute of Biology at the Humboldt University in Berlin, Research Group Leader and guest professor at the University of Umeå, Sweden, Alexander von Humboldt Professor

Search terms
CRISPR/Cas9, Genome Editing, Jennifer Doudna

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1986-1992	Studied biology, microbiology, biochemistry and genetics at University Pierre et Marie Curie, Paris (UPMC)
1992-1997	Doctoral student at Pasteur Institute, post-doctoral student at Pasteur Institute and Rockefeller University, New York
1997-1999	Assistant Research Scientist at New York University Medical Center
1999-2002	Research Associate at St. Jude Children's Research Hospital, Memphis and at the Skirball Institute of Biomolecular Medicine, New York
2002-2004	Research Group Leader and visiting professor at the Institute of Microbiology and Genetics, University of Vienna
2004-2006	Research Group Leader and Assistant Professor, University of Vienna
2006	Senior Lecturer for microbiology and habilitation at the Centre for Molecular Biology, University of Vienna
2006-2009	Research Group Leader and Associate Professor at Max F. Perutz Laboratories, Vienna
2009-2014	Research Group Leader and Associate Professor at the Laboratory for Molecular Infection Medicine Sweden (MIMS), University of Umeå, Sweden
2013	Lecturer in Medical Microbiology, University of Umeå
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since 2015	Director at the Max Planck Institute for Infection Biology, Berlin

The article *A Programmable Dual-RNA-Guided DNA Endonuclease in Adaptive Bacterial Immunity* was published in 2012. On five pages, the authors Emmanuelle Charpentier and Jennifer Doudna describe the defense system of the scarlet fever bacterium Streptococcus pyogenes: it uses a molecule-sized instrument that consists of a viewfinder and a kind of DNA scissor. The acronym for this defense system is CRISPR/Cas9, generally abbreviated to: CRISPR [pronounced: kris :: per]. The gene scissors of the streptococcal bacterium can be reconstructed, and its viewfinder set on any targets of the DNA sequence.

DOLLY, THE CLONED SHEEP

Well bleated, sheep!

Shortened article from: ZEIT ONLINE, dpa: July 5, 2016, 3:15 p.m., by Alina Schadwinkel

When Dolly the cloned sheep was presented to the public in February 1997, fear of genetic engineering was huge. And today? We clone breeding animals in the agricultural industry.

Name: 6LL3, known as Dolly
Famous because: the first mammal cloned from an adult cell
Current location: National Museum of Scotland, stuffed

This sheep was born a star. On July 5, 1996, Dolly was born just as all lambs are. However, she had been created five months earlier in a test tube as sample 6LL3. She developed from the genetic material of a body cell, not from a fertilized egg cell. Dolly was therefore the first copy of an adult sheep. And the excitement was huge. (...)

The opportunities offered by cloning had been overestimated

Proponents of technology hoped for cures for diseases such as cancer or Alzheimer's through cloning. Sceptics, on the other hand, warned of a horror-film technology that could one day lead to the mass production of cloned people. This much we now know: The risks and opportunities of the technology had been greatly overestimated. (...)

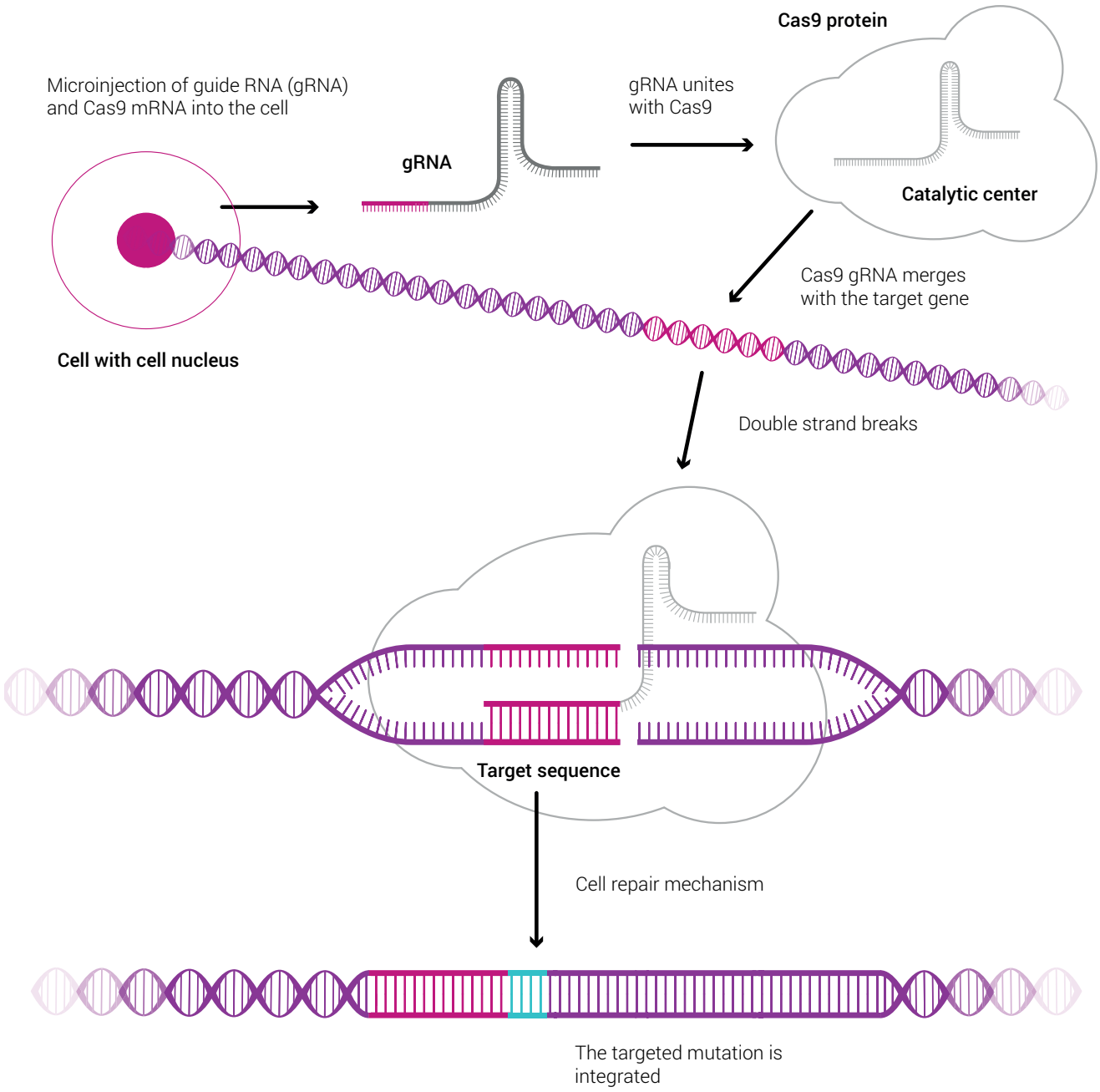
In a nutshell, the cell nucleus transfer method can be described as follows: The researchers took an oocyte, i.e. an unfertilized egg, and removed the chromosomes. Then they took a complete cell containing both male and female chromosomes. They then fused the cell with the empty cell, stimulated growth and implanted it in a surrogate mother. (...)

The researchers claim to have transferred a total of 277 cell nuclei from a Finn Dorset sheep to the oocytes of a Scottish Blackface. Only 29 of the resulting embryos were implanted in the surrogate mother. Expectations were low, reports Nature: It seemed almost impossible for the nucleus of an adult cell to be reprogrammed such that a living animal would grow from it. Most of the cloned embryos died, many even before the researchers could confirm the pregnancy using ultrasound. In Dolly's case, however, all went well. At around 4:30 p.m. on July 5, 1996, the surrogate mother began contractions. Half an hour after the birth the doppelgänger sheep stood for the first time. (...)

The technology has hardly developed since then. It turned out to be generally useless. For example, in regenerative medicine, other methods are more promising; as a human reproductive technology, cloning is taboo worldwide – and in animals the success rate is rather low. In addition, clones appear to be vulnerable: Dolly died at the age of six from an incurable lung disease that usually only occurs in older animals.

Cloning is too expensive for mass production. Only for duplicating award-winning breeding animals has the cloning technique managed to make a foothold. Since mass production of cloned animals would be too expensive and time-consuming, industry relies more on cloning animals with extraordinary genes, which should then provide genetically high-quality offspring. While cloning for agriculture in the EU is subject to strict licensing regulations and is therefore not practiced, companies do use it in other countries. Interest in the USA is particularly great, where, in 2009, the FDA licensing agency found that the consumption of cloned farm animals was absolutely safe. There is no labelling obligation for meat or milk derived from cloned animals. Since then, critics have feared that some products could end up undetected in the European market.

Finally, last year, the European Parliament demanded a far-reaching ban on cloning. This should not only apply to cloned animals themselves, but also to their offspring. It is also intended to prohibit the import of products from clones, such as milk, as well as semen and ova from cloned breeding animals. A vote by the Council of Ministers, which has yet to reach a unified position, is still pending. Parliament and the Council of Ministers must then decide together. Twenty years after Dolly's birth. Congratulations.



APPLICATIONS

1. Research and medicine

- disease models
- basic research and knowledge gains
- gene therapy for hereditary diseases, infectious diseases and cancer

2. Biotechnology

- seeds
- livestock
- gene drive against malaria mosquitoes (defective genes are rapidly spread through the population by the gene drive system)

3. Designer organisms

Adaptation of human embryos, sperm and eggs against genetic disorders – can babies be designed with the desired characteristics in the future? Can scientific amateurs also use the procedure to design organisms on a whim?

About the lesson series "Understanding Stem Cells - The Conference for Schools"

In this four-part series of lessons, the German Stem Cell Network and the Ernst Schering Foundation provide teachers with fact-checked knowledge about stem cells. The freely usable material allows students from 14 years onwards to actively immerse themselves in current research. The scientific experts at the German Stem Cell Network ensure the technical and professional quality of the material.The Schering Foundation uses its experience in science education to introduce young adults to current research topics using new methods and to encourage their interest in science. This material is available online at: http://www.understanding-stemcells.info

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