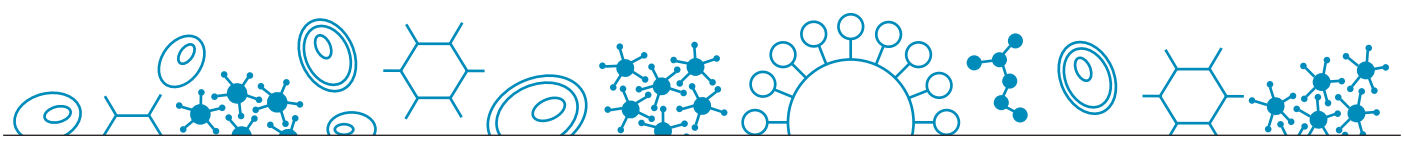
Understanding Stem Cells The Conference

3 Therapy



3 Therapy

In this module, the students develop the possible applications of stem cell research in medical therapies. As participants in a scientific conference, they prepare a data blitz session and an expert discussion.

90 minutes

Tasks:
Data Blitz Session
Meet the Expert

Material:
Data Blitz Session A–F
Meet the Expert A
Meet the Expert B
Meet the Expert C

Introduction

"Medicine has made great progress. Some of which has even benefited the patient."

Gerhard Kocher, Swiss political scientist, health economist and aphorist, born in 1939

Data Blitz Session

In five groups, the students each present a possible form of therapy based on stem cells. To do this, they receive a brief informational text, notes on additional research and a presentation structure with which they can briefly introduce the therapy research. One group member makes the presentation. The blitz lectures are presented one after the other.

30 minutes preparation
5 x 3 minutes presentation

5 small groups
Data Blitz Session exercise sheet
Data Blitz Session A - F material sheets

Meet the Expert

The students work on a case study and briefly present how the patient was treated. The other group asks questions about the case. Subsequently, the two therapies can be compared.

15 minutes preparation
2 x 10 minutes presentation
2 x 10 minutes questions

2 groups
Meet the Expert exercise sheet
Meet the Expert A material sheet
Meet the Expert B material sheet
Meet the Expert C material sheet

Outlook

"Our conference continues. In the next module we look at genetics, a field of research closely related to stem cell research."

Data Blitz Session

In a blitz session, the current state of research is introduced in short presentations. At conferences, guidelines specify how long these blitz presentations may be.

TASK Prepare a 3 minute presentation on your topic. In the data blitz session, all brief presentations are given one after the other.

OBJECTIVE **In your presentation, answer two questions:**

1. What is already possible?

2. What may be possible in the future?

TIP You can use this presentation structure for your short presentation:

Introduction:	... People get sick annually from ...
Thesis:	We can already help many of them.
Argument 1:	We can ...
Argument 2:	We are working on ...
Argument 3:	Risks involved are ...
Thesis:	In this way we can help patients with ....

Data-Blitz-topics

Data Blitz A: Skin burns

Data Blitz B: Liver failure Data

Data Blitz C: Corneal clouding Data

Data Blitz D: Diabetes

Data Blitz E: Leukemia

Data Blitz F: Parkinson's disease

Meet the Expert

Meet the Expert means that conference participants can interview recognized experts directly about their research.

TASK You are an expert and have brought a successful case study to the conference. Explain how you managed to help the patient.

OBJECTIVE **Your explanation should precisely explain the procedure.**

TIP Use a drawing during your explanation to clarify the procedure.

BONUS Compare the treatment of the two patients Jack Crick and Timothy Ray Brown. How do the treatments differ?

Expert topic

Expert A: Jack Crick: SCID-X1

Expert B: Timothy Ray Brown: HIV

Expert C: Hassan: Epidermolysis bullosa

Data Blitz A: Skin burns

Epidermal stem cells are among the few stem cell types that are already used in the treatment of patients. Thanks to a discovery made in the USA in 1970 by Professor Howard Green, epidermal stem cells can be taken from a patient, duplicated and used to grow new epidermis in the laboratory. This epidermis can then be used as a skin graft for the patient. In the interim, researchers in a laboratory have succeeded in growing up to 20 skin grafts of 60 square centimeters each in just three weeks from the cells of a small piece of skin. As the new skin was grown from the body's own cells, it is not rejected. The technique is mainly used to save the lives of patients who have suffered large-scale third-degree burns. Only a handful of clinical centers are capable of successfully performing this costly treatment. However, it is not an ideal solution. Using this method, only the epidermis can be replaced; the new skin has no skin appendages, such as hair follicles, sweat glands or sebaceous glands. In particular, the absence of the sweat glands affects the patients, as they do not have normal thermoregulation. Intensive research is being performed to improve the properties of the grown skin.

Read on:
https://www.eurostemcell.org/skin-stem-cells-where-do-they-live-and-what-can-they-do

Data Blitz B: Liver failure

For a long time, a liver transplant was the only treatment option for acute liver failure. This will hopefully change soon – thanks to stem cell therapy. Liver cells (hepatocytes) from the laboratory can be used as an interim solution. In order to transfer them to the liver cell culture, natural liver formation is being researched. Growth agents (cytokines) are added and reagents are developed that will fine-tune cell characteristics of gene expression. MicroRNAs, that is, non-coding RNA molecules, can also play an important role in this process. The advantage of this procedure: The patient's own cells are used, meaning that no immunosuppressant drugs are necessary. Research is also being carried out to convert the body's own connective tissue cells in the liver into hepatocytes, allowing them to participate in the healing process.
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Find out more:
GSCN video: Stem cell therapie of the liver
https://www.youtube.com/watch?time_continue=4&v=LVJZxZp8W9I&feature=emb_logo

Data Blitz C: Corneal clouding

James Funderburgh of the University of Pittsburgh, together with ophthalmologists from India, investigated whether stem cells could be used to heal corneal injuries. For their experiments, they originally used the limbus stem cells of deceased people. The limbus is the transition zone between the cornea and the dermis in the eyeball. Today, for clinical applications, the cells are taken from the patient's healthy eye limbus. According to the researchers, such a biopsy can be kept so small that it does not endanger the healthy eye. The cells are then first multiplied in the laboratory, which is easily possible today. The stem cells are then applied directly to the injured cornea using a fibrin glue. Transparency and vision returns within four weeks. In the meantime, the product Holoclar, which was approved for patient treatment on the European market, has become available for these treatment options.

Read further:
http://www.eurostemcell.org/story/europe-approves-holoclar-first-stem-cell-based-medicinal-product

Data Blitz D: Leukemia

In leukemia, blood stem cells have lost their ability to differentiate correctly. The cells renew themselves without becoming specialists. The leukemia cells produce white precursor cells that do not mature and are not functional. They spread within the bone marrow and interfere with normal blood formation. As a consequence, the blood no longer carries enough oxygen and loses its wound healing function. Blood stem cells are transplanted to treat leukemia. In the process, the autologous blood stem cells causing the leukemia are destroyed with all hematopoietic cells through high doses of chemotherapy or radiation. In a second step, the blood stem cells previously obtained from the patient are returned (autologous) or transplanted from a suitable donor (allogeneic). Allogeneic stem cell transplantation is necessary if the leukemia has developed in the patient's own blood stem cells. However, it carries the risk of graft-versus-host disease (GvHD), in which the immune cells of the donor attack the patient's organs.

Find out more:
GSCN video: Cell therapy with CRISPR/Cas?
https://www.youtube.com/watch?v=_-wEh-33Uio&feature=emb_logo

Data Blitz E: Diabetes

Douglas Melton's children have diabetes and need to inject insulin. The internationally-renowned Harvard professor intends to change this.

From the Neue Zürcher Zeitung, Oct. 7, 2016:
"In type 1 diabetes, only one type of cell is missing, which in addition performs an absolutely crucial task in its organ, the pancreas: measure the blood sugar level and, if necessary, dispense insulin. This must be cured by replacement cells grown in the laboratory," says Melton, was convinced even back then. So, he began growing these replacement cells. (...)

It would take until 2014 for the Harvard team to make functioning beta cells from embryonic stem cells as well as from iPS cells – the hoped for breakthrough. The grown beta cells measure glucose concentrations, produce insulin and emit it when needed. This works both in the artificial environment of a Petri dish and in diabetic mice. Elsewhere in the world, other researchers were also working toward this goal, but no one was faster than Melton. Some also try to reprogram cells into beta cells directly within the pancreas.

"There are at least 70 proteins in the body that control the development and specialization of body cells from embryonic stem cells. We had to find those that create beta cells, in the correct temporal combination and concentration," says Melton, describing the greatest hurdle.

Other questions also remain unanswered. It is still unclear whether iPS or embryonic stem cells are the better source material. For standardized therapies, the latter will probably prevail, because once here, a stem cell line and the beta cells grown from it can be subjected to all safety checks and then be used in every patient. When using iPS cells derived from the patient to be treated, the safety tests would need to be performed individually for each patient – too costly and expensive for clinical use.

In addition, we do not yet know how many newly grown beta cells we need to control blood sugar levels and how long they will work in the body. Answers to such questions could be provided by the world's first attempt to treat diabetes using replacement cells, started in late-2014 by the California company ViaCyte. In the process, beta-cell precursors grown from stem cells and packaged in biopolymer capsules were implanted. According to the company, initial results reveal that at least some of the implanted cells are mature after 12 weeks. How well they work and how long they will survive is still uncertain."

Data Blitz F: Parkinson's disease
Replacing lost cells

Physicians and scientists are of the opinion that cell replacement therapy can also work for the neurodegenerative Parkinson's disease, citing the results of transplantation studies conducted in the 1980s. Scandinavian scientists had transplanted adrenal cells into the brains of four Parkinson's disease patients. The adrenal glands are located on the kidneys and contain cells that produce dopamine and similar substances. Following transplantation, some improvement occurred in the condition of the patients, but was, however, slight and did not last long. This was the first transplantation of dopamine-producing tissue into the human brain. In subsequent tests, scientists from Sweden, the USA and Canada transplanted dopamine-producing neurons from human fetuses into animals and patients and thereby achieved some crucial, but only modest, improvements. One group of patients suffered side effects and, in some cases, more than a decade after the procedure, the disease was also transferred to the transplanted fetal cells.

Scientists still hope to delay the onset or slow down the advance of Parkinson's disease by introducing cells from early stages of human development into the brain. However, there is insufficient fetal tissue available to treat the large number of Parkinson's disease patients. In addition, the use of fetuses poses ethical questions. Stem cells could serve as an alternative source of new cells for Parkinson's disease patients. Embryonic stem cells (ES) could be made to produce dopamine-producing neurons that would be transplanted into the patient. In the laboratory, dopamine-producing neurons have been produced both from embryonic stem cells from mice and from humans. Induced pluripotent stem cells (iPS) could be prepared in the laboratory from differentiated skin cells of patients and then be used to form dopamine-producing neurons. In 2010, American scientists treated rats with neurons produced from human skin cells using the iPS procedure. The transplanted neurons caused a reduction in Parkinson's disease symptoms in the rats. However, mice and rats require fewer neurons than humans, and it remains questionable whether this approach will work in humans – clinical trials to test this are in preparation worldwide. Furthermore, additional studies are required to demonstrate that treatment using the cells is safe and does not cause brain tumors.

Read on:
https://www.eurostemcell.org/parkinsons-disease-how-could-stem-cells-help

Patient Jack Crick

2004	Born in May
2004	X-SCID is diagnosed in September. The search for a suitable bone marrow donor unsuccessful. Gene therapy using the patient's own blood stem cells is successful, even without chemotherapy.
2011	Patient has had no symptoms since.

Attending Physician

Bobby Gaspar, Great Osmond Street Hospital, London

X-SCID

SCID stands for severe combined immunodeficiency;
A weakening of the immune system due to the absence or lack of lymphocyte function; mutations in genetic information (DNA) cause the disruption of T cell development. The patients' immune systems cannot cope with the pathogens in our normal environment and the affected children must therefore live in a sterile environment.

Therapy

Collection of hematopoietic stem cells (CD34-positive); inserting the corrected gene into the test tube using a retroviral vector (taken from the mouse leukemia virus); stem cells are returned to the patient.
Advantages: Use of own cells instead of foreign cells; low risk of rejection or incompatibility; no suitable donor necessary.

Discussion

The introduction of a new gene can lead to changes in cell properties or to degeneration (cancer). Cases are known where patients developed leukemia. The trigger seems to be the retroviral vector. Research is being carried out on the use of newer HIV-derived lentiviral vectors, for example, which have a much better safety profile.

Search terms
Bubble Boy, David Vetter

Patient Timothy Ray Brown

1966	Born in Seattle, USA
1995	Diagnosis: HIV positive
until 2006	Treatment using highly active antiretroviral therapy (HAART): 600 mg Efavirenz, 200 mg Emtricitabine and 300 mg Tenofovir
2006	Diagnosis of acute myeloid leukemia (AML); chemotherapy treatment
2007	Treatment by allogeneic stem cell transplantation from a donor with a mutation in the CCR5 cell surface receptor. The mutation prevents the HI virus from penetrating the cells.
since 2007	HI virus no longer detectable using common procedures
2008	Leukemia identified again; second stem cell transplantation (same donor)
since 2008	HI virus undetectable using common procedures; leukemia treatment successful; neurological disorders diagnosed

HLA type: B57

Attending Physician

Dr. Gero Hütter, Benjamin Franklin Campus Charité Berlin (until 2009)

Bone marrow donor

HLA type: B57

Mutation: delta 32 on receptor CCR5

Therapy

Transplantation of allogeneic stem cell transplantation of a donor with a mutation in the cell surface receptor CCR5. The mutation prevents the HI virus from entering the cells.

Discussion

It is not clear whether this individual case is reproducible. The procedure is very expensive. In 2012, Steven Yukl (University of California, San Francisco) investigated nine billion patient blood cells using polymerase chain reaction (PCR). After several attempts he identifies fragments of the virus genome in the blood plasma. Douglas Richman (University of California, San Diego) also conducts blood tests and finds no residues. He considers contamination in the Yukl test possible; in addition, PCR is highly sensitive and error-prone.

Search terms

The Berlin Patient, Mississippi Baby, The London Patient

Patient Hassan

Born in 2008	started treatment at the age of 7
2015:	After fleeing from Syria to Germany, he suffered infections and chronic skin lesions as a result of the inherited disorder epidermolysis bullosa.
2015-2016:	Skin graft involving 80 percent of the patient's skin. Since then, the patient has been largely free of symptoms.

Doctors involved

Tobias Rothoeft, Kinderklinik Bochum

Tobias Hirsch, Universitätsklinikum Bergmannsheil (plastic surgeon)

Michele De Luca, Center for Regenerative Medicine at the University of Modena (stem cell researcher)

Epidermolysis bullosa

Epidermolysis bullosa is an inherited disorder. Children with this condition are sometimes called butterfly children, because their skin is as fragile as a butterfly's wings. This is because the upper layer of the skin (epidermis) is not properly attached to the layer underneath (dermis). People with this disease have a defective LAMB3 gene. This gene encodes the laminin-332 protein.

Treatment

Skin cells from Hassan were sent to Italian experts in Modena for culturing. The scientists used retroviral vectors to insert a healthy LAMB3 gene into the skin cells. Retroviral vectors are viruses which have been specially modified to carry genes into cells. The genetically modified stem cells in the piece of skin were then cultured in a clean room laboratory to produce large pieces of skin suitable for grafting. Over a series of three operations in Germany, scientists then grafted the cultured tissue. In total, they replaced 80 percent of Hassan's skin.
The new skin contains roughly the same amount of the laminin-332 anchor protein as normal, healthy skin.

Discussion

There are around 35,000 children with epidermolysis bullosa in Europe. The severity of the disease varies greatly. Until now, no treatment aimed at eliminating the underlying cause of the condition has been available. All gene therapies carry a risk that the new gene could be inserted into the wrong place in the genome, however. This can disrupt cell regulatory processes and cause cancer.
The treatment Hassan underwent was risky and laborious. It was justified by the extent of his suffering and the fact that there was no prospect of his suffering being relieved by any other treatment.

Search terms

Patient Hassan, butterfly child
(https://www.spiegel.de/gesundheit/diagnose/gentherapie-junge-erhaelt-neue-haut-a-1177073.html)

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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