DOWNLOAD PDF III.8. GENERATING CANCER STEM CELLS FOR STUDY PURPOSES.

Chapter 1 : Pomegranate Extract Alters Breast Cancer Stem Cell Properties in

Procedure that uses nuclear transplantation to generate cells for tissue repair and other such purposes, as opposed to producing whole multicellular individuals. tight Junction Cell-cell junction that seals adjacent epithelial cells together, preventing the passage of most dissolved molecules from one side of the epithelial sheet to the other.

They can stay non-dividing and non-specific for years until the body summons them to repair or grow new tissue. Adult stem cells can divide or self-renew indefinitely. This means they can generate various cell types from the originating organ or even regenerate the original organ, entirely. This division and regeneration are how a skin wound heals, or how an organ such as the liver, for example, can repair itself after damage. In the past, scientists believed adult stem cells could only differentiate based on their tissue of origin. However, some evidence now suggests that they can differentiate to become other cell types, as well. Embryonic stem cells From the very earliest stage of pregnancy, after the sperm fertilizes the egg, an embryo forms. Around 3â€”5 days after a sperm fertilizes an egg, the embryo takes the form of a blastocyst or ball of cells. The blastocyst contains stem cells and will later implant in the womb. Embryonic stem cells come from a blastocyst that is 4â€”5 days old. When scientists take stem cells from embryos, these are usually extra embryos that result from in vitro fertilization IVF. In IVF clinics, the doctors fertilize several eggs in a test tube, to ensure that at least one survives. They will then implant a limited number of eggs to start a pregnancy. When a sperm fertilizes an egg, these cells combine to form a single cell called a zygote. This single-celled zygote then starts to divide, forming 2, 4, 8, 16 cells, and so on. Now it is an embryo. Soon, and before the embryo implants in the uterus, this mass of around â€” cells is the blastocyst. The blastocyst consists of two parts: Scientists call these totipotent cells. The term totipotent refer to the fact that they have total potential to develop into any cell in the body. With the right stimulation, the cells can become blood cells, skin cells, and all the other cell types that a body needs. In early pregnancy, the blastocyst stage continues for about 5 days before the embryo implants in the uterus, or womb. At this stage, stem cells begin to differentiate. Embryonic stem cells can differentiate into more cell types than adult stem cells. Scientists have used MSCs to create new body tissues, such as bone, cartilage, and fat cells. They may one day play a role in solving a wide range of health problems. Induced pluripotent stem cells iPS Scientists create these in a lab, using skin cells and other tissue-specific cells. These cells behave in a similar way to embryonic stem cells, so they could be useful for developing a range of therapies. However, more research and development is necessary. To grow stem cells, scientists first extract samples from adult tissue or an embryo. They then place these cells in a controlled culture where they will divide and reproduce but not specialize further. Stem cells that are dividing and reproducing in a controlled culture are called a stem-cell line. Researchers manage and share stem-cell lines for different purposes. They can stimulate the stem cells to specialize in a particular way. This process is known as directed differentiation. Until now, it has been easier to grow large numbers of embryonic stem cells than adult stem cells. However, scientists are making progress with both cell types. Types of stem cells Researchers categorize stem cells, according to their potential to differentiate into other types of cells. Embryonic stem cells are the most potent, as their job is to become every type of cell in the body. The full classification includes: These stem cells can differentiate into all possible cell types. The first few cells that appear as the zygote starts to divide are totipotent. These cells can turn into almost any cell. Cells from the early embryo are pluripotent. These cells can differentiate into a closely related family of cells. Adult hematopoietic stem cells, for example, can become red and white blood cells or platelets. These can differentiate into a few different cell types. Adult lymphoid or myeloid stem cells can do this. These can only produce cells of one kind, which is their own type. However, they are still stem cells because they can renew themselves. Examples include adult muscle stem cells. Embryonic stem cells are considered pluripotent instead of totipotent because they cannot become part of the extra-embryonic membranes or the placenta. Uses Transplants with stem cells are already helping people with diseases such as lymphoma. Stem cells themselves

do not serve any single purpose but are important for several reasons. First, with the right stimulation, many stem cells can take on the role of any type of cell, and they can regenerate damaged tissue, under the right conditions. This potential could save lives or repair wounds and tissue damage in people after an illness or injury. Scientists see many possible uses for stem cells. Tissue regeneration Tissue regeneration is probably the most important use of stem cells. Until now, a person who needed a new kidney, for example, had to wait for a donor and then undergo a transplant. There is a shortage of donor organs but, by instructing stem cells to differentiate in a certain way, scientists could use them to grow a specific tissue type or organ. They can then repair a severe burn or another injury by grafting this tissue onto the damaged skin, and new skin will grow back. Cardiovascular disease treatment In , a team of researchers from Massachusetts General Hospital reported in PNAS Early Edition that they had created blood vessels in laboratory mice, using human stem cells. Within 2 weeks of implanting the stem cells, networks of blood-perfused vessels had formed. The quality of these new blood vessels was as good as the nearby natural ones. The authors hoped that this type of technique could eventually help to treat people with cardiovascular and vascular diseases. Scientists could use stem cells to replenish the damaged brain tissue. This could bring back the specialized brain cells that stop the uncontrolled muscle movements. Researchers have already tried differentiating embryonic stem cells into these types of cells, so treatments are promising. Cell deficiency therapy Scientists hope one day to be able to develop healthy heart cells in a laboratory that they can transplant into people with heart disease. These new cells could repair heart damage by repopulating the heart with healthy tissue. Similarly, people with type I diabetes could receive pancreatic cells to replace the insulin-producing cells that their own immune systems have lost or destroyed. The only current therapy is a pancreatic transplant, and very few pancreases are available for transplant. Blood disease treatments Doctors now routinely use adult hematopoietic stem cells to treat diseases, such as leukemia , sickle cell anemia , and other immunodeficiency problems. Hematopoietic stem cells occur in blood and bone marrow and can produce all blood cell types, including red blood cells that carry oxygen and white blood cells that fight disease. Donating or harvesting stem cells People can donate stem cells to help a loved one, or possibly for their own use in the future. Donations can come from the following sources: These cells are taken under a general anesthetic, usually from the hip or pelvic bone. Technicians then isolate the stem cells from the bone marrow for storage or donation. A person receives several injections that cause their bone marrow to release stem cells into the blood. Next, blood is removed from the body, a machine separates out the stem cells, and doctors return the blood to the body. Stem cells can be harvested from the umbilical cord after delivery, with no harm to the baby. Some people donate the cord blood, and others store it. This harvesting of stem cells can be expensive, but the advantages for future needs include:

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Chapter 2 : Stem-cell therapy - Wikipedia

In stem cell transplants, stem cells replace cells damaged by chemotherapy or disease or serve as a way for the donor's immune system to fight some types of cancer and blood-related diseases, such as leukemia, lymphoma, neuroblastoma and multiple myeloma.

What are embryonic stem cells? What stages of early embryonic development are important for generating embryonic stem cells? Embryonic stem cells , as their name suggests, are derived from embryos. Most embryonic stem cells are derived from embryos that develop from eggs that have been fertilized in vitro â€"in an in vitro fertilization clinicâ€"and then donated for research purposes with informed consent of the donors. How are embryonic stem cells grown in the laboratory? Growing cells in the laboratory is known as cell culture. The cells divide and spread over the surface of the dish. This coating layer of cells is called a feeder layer. The mouse cells in the bottom of the culture dish provide the cells a sticky surface to which they can attach. Also, the feeder cells release nutrients into the culture medium. This is a significant scientific advance because of the risk that viruses or other macromolecules in the mouse cells may be transmitted to the human cells. The process of generating an embryonic stem cell line is somewhat inefficient, so lines are not produced each time cells from the preimplantation-stage embryo are placed into a culture dish. However, if the plated cells survive, divide and multiply enough to crowd the dish, they are removed gently and plated into several fresh culture dishes. The process of re-plating or subculturing the cells is repeated many times and for many months. Each cycle of subculturing the cells is referred to as a passage. Once the cell line is established, the original cells yield millions of embryonic stem cells. Embryonic stem cells that have proliferated in cell culture for six or more months without differentiating, are pluripotent , and appear genetically normal are referred to as an embryonic stem cell line. At any stage in the process, batches of cells can be frozen and shipped to other laboratories for further culture and experimentation. What laboratory tests are used to identify embryonic stem cells? At various points during the process of generating embryonic stem cell lines, scientists test the cells to see whether they exhibit the fundamental properties that make them embryonic stem cells. This process is called characterization. However, laboratories that grow human embryonic stem cell lines use several kinds of tests, including: Growing and subculturing the stem cells for many months. This ensures that the cells are capable of long-term growth and self-renewal. Scientists inspect the cultures through a microscope to see that the cells look healthy and remain undifferentiated. Using specific techniques to determine the presence of transcription factors that are typically produced by undifferentiated cells. Transcription factors help turn genes on and off at the right time, which is an important part of the processes of cell differentiation and embryonic development. In this case, both Oct 4 and Nanog are associated with maintaining the stem cells in an undifferentiated state, capable of self-renewal. Using specific techniques to determine the presence of particular cell surface markers that are typically produced by undifferentiated cells. Examining the chromosomes under a microscope. This is a method to assess whether the chromosomes are damaged or if the number of chromosomes has changed. It does not detect genetic mutations in the cells. Determining whether the cells can be re-grown, or subcultured, after freezing, thawing, and re-plating. Testing whether the human embryonic stem cells are pluripotent by 1 allowing the cells to differentiate spontaneously in cell culture; 2 manipulating the cells so they will differentiate to form cells characteristic of the three germ layers ; or 3 injecting the cells into a mouse with a suppressed immune system to test for the formation of a benign tumor called a teratoma. Teratomas typically contain a mixture of many differentiated or partly differentiated cell typesâ€"an indication that the embryonic stem cells are capable of differentiating into multiple cell types. How are embryonic stem cells stimulated to differentiate? As long as the embryonic stem cells in culture are grown under appropriate conditions, they can remain undifferentiated unspecialized. But if cells are allowed to clump together to form embryoid bodies , they begin to differentiate spontaneously. They can form muscle cells, nerve cells, and many other cell types. Although spontaneous differentiation is a good

indication that a culture of embryonic stem cells is healthy, the process is uncontrolled and therefore an inefficient strategy to produce cultures of specific cell types. So, to generate cultures of specific types of differentiated cellsâ€”heart muscle cells, blood cells, or nerve cells, for exampleâ€”scientists try to control the differentiation of embryonic stem cells. They change the chemical composition of the culture medium, alter the surface of the culture dish, or modify the cells by inserting specific genes. Through years of experimentation, scientists have established some basic protocols or "recipes" for the directed differentiation of embryonic stem cells into some specific cell types Figure 1. For additional examples of directed differentiation of embryonic stem cells, refer to the NIH stem cell report. Directed differentiation of mouse embryonic stem cells. Click here for larger image.

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Chapter 3 : Stem cells: Sources, types, and uses

Adult stem cells have the ability to make more stem cells and to generate the cells of a differentiated tissue. Skin stem cells can replenish the epidermis and make hair follicle cells. Skin grown in culture from just a few skin stem cells can be used to treat burn patients or replace damaged corneal epithelium.

Not all stem cells come from an early embryo. In fact, we have stem cells in our bodies all our lives. One way to think about stem cells is to divide them into three categories: You can read in detail about the properties of these different types of stem cells and current research work in our other fact sheets. Here, we give you a short overview of different stem cell types before comparing the progress made towards therapies for patients, and the challenges or limitations that still need to be addressed. Embryonic stem cells ESCs have unlimited potential to produce specialised cells of the body, which suggests enormous possibilities for disease research and for providing new therapies. ESCs are what is called pluripotent, that means they can differentiate into any cell type of the body. Human ESCs were first grown in the lab in The cells are derived from a developmental stage, when about cells form a so called blastocyst â€" a very early embryo. But not every experiment requires a new blastocyst. As of October , about different cell lines, each derived from a single embryo, were obtained in Europe source human pluripotent stem cell registry. These cell lines need to be very well characterised for scientists to use them in clinical trials or drug development â€" another reason which limits the number of embryonic stem cell lines. Current challenges facing ESC research include ethical considerations and the need to ensure that ESCs fully differentiate into the required specialised cells before transplantation into patients. It also allows the generation of iPSC cell banks, which would work almost like blood banks, where a matching donor can be found for patients. However, use of iPSCs in cell therapy is theoretical at the moment. The technology is very new and the reprogramming process is not yet well understood. Scientists need to find ways to produce iPSCs safely and more efficiently. The cells must also be shown to completely and consistently differentiate into the required types of specialised cells to meet standards suitable for use in patients. Many tissues in the human body are maintained and repaired throughout life by stem cells. These tissue stem cells are very different from embryonic stem cells. Tissue stem cells, are not pluripotent like ESCS, but multipotent. That means they can only make a limited number of specialised cell types that are specific for their organ of origin; neural stem cells, for example, can only differentiate into specialised brain cells, whereas blood stem cells can only form specialised cells of the blood system. Stem cells are important tools for disease research and offer great potential for use in the clinic. Some adult stem cell sources are currently used for therapy, although they have limitations. The first clinical trials using cells made from embryonic stem cells have just finished, but further studies are needed before any therapeutics for more patients can be approved. Meanwhile, induced pluripotent stem cells are already of great use in research, but a lot of work is needed before they can be considered for use in the clinic. All other clinical trials rather involve the derivation of iPSCs from patient cells either for disease modelling, drug testing or to increase our understanding of the basic biology of this cell type. An additional avenue of current research is transdifferentiation â€" converting one type of specialised cell directly into another. All these different research approaches are important if stem cell research is to achieve its potential for delivering therapies for many debilitating diseases.

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Chapter 4 : Scientists generate a new type of human stem cell that has half a genome | EurekAlert! Scienc

"This study has given us a new type of human stem cell that will have an important impact on human genetic and medical research," said Nissim Benvenisty, MD, PhD, Director of the Azrieli Center for Stem Cells and Genetic Research at the Hebrew University of Jerusalem and principal co-author of the study.

Visit our Re-post guidelines Following on the heels of recent revelations that x-ray mammography may be contributing to an epidemic of future radiation-induced breast cancers, in a new article titled, " Radiation Treatment Generates Therapy Resistant Cancer Stem Cells From Aggressive Breast Cancer Cells ," published in the journal Cancer July 1st, , researchers from the Department of Radiation Oncology at the UCLA Jonsson Comprehensive Cancer Center report that radiation treatment actually drives breast cancer cells into greater malignancy. The researchers found that even when radiation kills half of the tumor cells treated, the surviving cells which are resistant to treatment, known as induced breast cancer stem cells iBCSCs , were up to 30 times more likely to form tumors than the nonirradiated breast cancer cells. In other words, the radiation treatment regresses the total population of cancer cells, generating the false appearance that the treatment is working, but actually increases the ratio of highly malignant to benign cells within that tumor, eventually leading to the iatrogenic treatment-induced death of the patient. Last month, a related study published in the journal Stem Cells titled, "Radiation-induced reprogramming of breast cells," found that ionizing radiation reprogrammed less malignant more differentiated breast cancer cells into iBCSCs, helping to explain why conventional treatment actually enriches the tumor population with higher levels of treatment-resistant cells. The primary reason for this is the fact that cancer stem cells, which are almost exclusively resistant to conventional treatment, are not being targeted, but to the contrary, are encouraged to thrive when exposed to chemotherapy and radiotherapy. In order to understand how conventional treatment drives the cancer into greater malignancy, we must first understand what cancer is They are capable of building their own blood supply angiogenesis , are able to defend themselves by silencing cancer-suppression genes, secreting corrosive enzymes to move freely throughout the body, alter their metabolism to live in low oxygen and acidic environments, and know how to remove their own surface-receptor proteins to escape detection by white blood cells. Because tumors are not simply the result of one or more mutated cells "going rogue" and producing exact clones of itself multi-mutational and clonal hypotheses , but are a diverse group of cells having radically different phenotypal characteristics, chemotherapy and radiation will affect each cell type differently. Tumors are composed of a wide range of cells, many of which are entirely benign. The most deadly cell type within a tumor or blood cancer, known as cancer stem cells CSCs , has the ability to give rise to all the cell types found within that cancer. They are capable of dividing by mitosis to form either two stem cells increasing the size of the stem population , or one daughter cell that goes on to differentiate into a variety of cell types, and one daughter cell that retains stem-cell properties. This means CSCs are tumorigenic tumor-forming and should be the primary target of cancer treatment because they are capable of both initiating and sustaining cancer. They are also increasingly recognized to be the cause of relapse and metastasis following conventional treatment. CSCs are exceptionally resistant to conventional treatment for the following reasons CSCs account for less than 1 in 10, cells within a particular cancer, making them difficult to destroy without destroying the vast majority of other cells comprising the tumor. Conventional chemotherapies target differentiated and differentiating cells, which form the bulk of the tumor, but these are unable to generate new cells like the CSCs which are undifferentiated. The existence of CSCs explains why conventional cancer treatment has completely missed the boat when it comes to targeting the root cause of tumors. One reason for this is because existing cancer treatments have mostly been developed in animal models where the goal is to shrink a tumor. Because mice are most often used and their life spans do not exceed two years, tumor relapse is very difficult, if not impossible to study. The first round of chemotherapy never kills the entire tumor, but only a percentage. This phenomenon is called the fractional kill. The goal is to use repeated treatment cycles

usually six to regress the tumor population down to zero, without killing the patient. This is not unlike what happens when antibiotics are used to treat certain infections. The drug may wipe out The reality is that the chemotherapy, even though it has reduced the tumor volume, by increasing the ratio of CSCs to benign daughter cells, has actually made the cancer more malignant. Radiotherapy has also been shown to increase cancer stem cells in the prostate, ultimately resulting in cancer recurrence and worsened prognosis. High margin of safety: Relative to chemotherapy agents such as 5-fluorouracil natural compounds are two orders of magnitude safer Selective Cytotoxicity: The ability to target only those cells that are cancerous and not healthy cells CSCs Targeting: The ability to target the cancer stem cells within a tumor population. The primary reason why these substances are not used in conventional treatment is because they are not patentable, nor profitable. Sadly, the criteria for drug selection are not safety, effectiveness, accessibility and affordability. If this were so, natural compounds would form an integral part of the standard of care in modern cancer treatment. Research indicates that the following compounds along with common dietary sources have the ability to target CSCs:

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Chapter 5 : Therapeutic cloning: promises and issues

Scientists have developed a new method that turns cells into stem cells by 'squeezing' them. The method paves the way for large-scale production of stem cells for medical purposes. EPFL scientists.

Sc is graduating this year with an Honours degree in Biochemistry. She is looking forward to studying medicine at McGill this year, and hopes to do more research in the future. For details, please refer to http: Abstract Advances in biotechnology necessitate both an understanding of scientific principles and ethical implications to be clinically applicable in medicine. In this regard, therapeutic cloning offers significant potential in regenerative medicine by circumventing immunorejection, and in the cure of genetic disorders when used in conjunction with gene therapy. Scientific roadblocks impeding advancement in therapeutic cloning are tumorigenicity, epigenetic reprogramming, mitochondrial heteroplasmy, interspecies pathogen transfer, low oocyte availability. Therapeutic cloning is also often tied to ethical considerations concerning the source, destruction and moral status of IVF embryos based on the argument of potential. Legislative and funding issues are also addressed. Future considerations would include a distinction between therapeutic and reproductive cloning in legislative formulations. Therapeutic cloning is the transfer of nuclear material isolated from a somatic cell into an enucleated oocyte in the goal of deriving embryonic cell lines with the same genome as the nuclear donor. Somatic cell nuclear transfer SCNT products have histological compatibility with the nuclear donor, which circumvents, in clinical applications, the use of immunosuppressive drugs with heavy side-effects. While the goal of reproductive cloning is the creation of a person, the purpose of therapeutic cloning is to generate and direct the differentiation of patient-specific cell lines isolated from an embryo not intended for transfer in utero. Therapeutic cloning, through the production of these autologous nuclear-transfer embryonic stem cells ntESC , offers great promises for regenerative and reproductive medicine, and in gene therapy, as a vector for gene-delivery. This review focuses on the recent breakthroughs in research based on therapeutic cloning, their feasibility, and their potential applications in medicine. The second part of this review discusses current roadblocks of therapeutic cloning, both in science and biomedical ethics, as well as the main alternatives to therapeutic cloning. The host oocyte is arrested at metaphase II 2 , and immobilized through light suction exerted by a pipette tip. A glass needle is used to remove a small piece of the zona pellucida and is reinserted through this puncture to extract the polar body and the oocyte nuclei. The incorporation of the somatic nuclei into the enucleated oocyte can be done through electrofusion, which is the application of an electric pulse to incorporate a mammalian cell into the oocyte used to produce Dolly. Alternatively, a somatic nucleus can be injected in the perivitelline space, the fluid-filled region between the zona pellucida and the ooplasm, as was used for Cumulina, the first mouse cloned through SCNT. Mitosis occurs in vitro until the formation of the blastocyst, a fluid-filled hollow ball of cells 40â€” cells to which is attached, from the inside, the embryoblast or inner cell mass from which ntESC are taken. Subsequent addition of cell-type specific markers and growth hormones promotes the differentiation of the ntESC into the desired cell-line to be implanted in vivo inside the nuclear donor for therapeutic purposes, in cell replacement therapy for instance. In vitro, the ESC can proliferate ad infinitum and are totipotent, capable of differentiating into any cell-type of the body, contrary to adult stem cells which are multipotent, namely committed to produce any type of cells pertaining to a particular lineage 3. Current legal status of therapeutic cloning in relation to reproductive cloning Laws regarding biomedicine are generally formulated in vague terms that do not distinguish reproductive from therapeutic cloning. The legitimacy of the latter is being questioned by the Prolife movement under the pretext that they were not democratically elected 5. Australia is currently reviewing its existing laws 7 to follow the Asian trend in Singapore, China and South Korea, and to legalize the generation of chimeras using human DNA. Since both reproductive and therapeutic cloning require the in vitro generation of a human embryo, prohibiting reproductive cloning is likely to result in severely hindering medically important research based on therapeutic cloning. A worldwide ban on

reproductive human cloning was proposed by France and Germany to the UN in and effective4 since September 4. A breakthrough in reproductive cloning was published a month earlier by Zavos and Illmensee, who injected a skin fibroblast nucleus from an infertile man into an oocyte provided by his wife. Promises of therapeutic cloning SCNT in the context of therapeutic cloning holds a huge potential for research and clinical applications including the use of SCNT product as a vector for gene delivery, the creation of animal models of human diseases, and cell replacement therapy in regenerative medicine. Furthermore, SCNT might, in the future, allow in vitro organogenesis and counteract senescence. The combination of therapeutic cloning and gene therapy offers a great potential for patient-specific rescue of a genetic mutation of the loss-of-function type, resulting in lowered or eliminated activity of a particular protein. Therapeutic cloning used in cell replacement therapy has the potential to create various types of tissues such as osteoblasts to counteract osteoporosis, and spinal cord regeneration following trauma, as shown by Deshpande et al, who transferred motor neurons derived from ESC to rats with a severed spinal cord 9. The resulting recovery of motility could lead to clinical applications for paralysis in humans through therapeutic cloning. Applications in regenerative medicine: The assembly of patient-specific cardiomyocytes, blood vessels and skin pieces fixed on a scaffold 39 holds great hope in the treatment of infarctus, atherosclerosis and severe burns, respectively. Consequently, the feasibility of de novo organogenesis based on SCNT depends on the elucidation of the tissue-specific molecular pathways mediating differentiation as well as the improvement of current SCNT and tissue engineering methods in order to recreate in vitro the complex three-dimensional organization and different intercellular interactions in organogenesis. The combination of growth factors and differentiation markers added at each stage of the method were designed to duplicate pancreatic organogenesis in vivo, a breakthrough which could concretize the hope of generating organs using therapeutic cloning. Barberi et al derived, by SCNT with somatic nuclei from mouse cumulus and tail-tip cells, two ntESC lines which were induced to differentiate into motor, GABAminergic, serotonergic and dopaminergic neurons 11 forming synapses and displaying normal electrophysiological properties in vitro. The dopaminergic neurons were directly injected into the cortical striatum of mice with Parkinson-like lesions induced by 6-hydroxydopamine. The rejuvenating potential conferred by SCNT can be paradoxically thwarted by telomere shortening, which reflects both the biological age of the nuclear donor and the time during which the ntESC lines were grown 37 , leading to premature aging also observed in cloned animals. However, the addition of a transgene containing the two coding regions needed for the production of telomerase could restore telomere lengths and thus increase the survival of the transplanted cells, which would increase the success rate of therapeutic cloning for regenerative medicine. Although a viable nonhuman primate has not yet been produced by SCNT, the success of Mitalipov and Wolf in creating a monkey by embryonic cloning from the nucleus of an allogenic blastomere supported the possibility that, through gene targeting, genetic defects can be reproduced in a wild-type genome to express a loss of function Hence, we are getting one step closer to patient-specific genetic engineering of animal models of human disease. Hence, clinical testing would be done on the animal model to find an optimal treatment, such as the drug combination to treat epigenetically-triggered cancer, highly variable among instances. The epigenetic modifications of chromatin structure in cancerous cells involve altered histone methylation, phosphorylation and deacetylation, as well as DNA methylation, which are reversible unlike genetic mutations. Supportive evidence for oncogenesis resulting from epigenetic features includes studies where normal mice blastula were obtained through SCNT from a skin malignancy 16 and a medullar tumor These studies could lead to clinical applications for cancer diagnosis in humans since nuclear reprogramming signals from the host ooplasm variably reset the epigenetic profile of the nuclear donor DNA. The derivation through SCNT of a healthy patient-specific stem line would show that cancer onset was triggered by epigenetic alterations. However, epigenetic resetting 15 following SCNT is likely to disrupt normal phenotype of the embryo-derived cell lines and the adult clone, the latter displaying an abnormally low body weight and expression level of MUP encoding genes Major Urinary Proteins as shown by Reik et al in the mouse. The epigenetic pattern of imprinted genes that was established during gametogenesis is lost

through SCNT 20 and the inactivation of early genes directing embryogenesis can explain low embryo viability and poor efficiency in the derivation of autologous ntESC lines. Blelloch et al found out, from studies on neurons, that stem cells used as the nuclear donor have a higher success rate 21 than fully differentiated cells in the derivation of autologous embryonic cells. For instance, patient-specific cardiomyocytes produced through SCNT will not integrate into the scarred heart tissue resulting from myocardial infarction. For instance, Duchenne Muscular Dystrophy DMD is an inheritable X-linked condition characterized by reduced intramuscular dystophin levels, causing cellular necrosis and weakening Being a single-gene disorder, DMD can be treated by therapeutic cloning in combination with gene therapy to restore normal dystrophin production. In the case where ntESC are transplanted without prior differentiation in vitro, the insertion of a transgene encoding MyoD 35 , a transcription factor responsible for commitment to the myogenic lineage, may promote muscle regeneration. The combination of gene therapy and therapeutic cloning has exciting potential for the genetic rescue of missing alleles in heritable genetic disorders such as severe combined immunodeficiency SCID , in which genetic mutations of specific genes such as RAG-1 and 2, essential for the DNA recombination allowing immunoglobulin and lymphocyte polymorphism, render the immune system completely inefficient. Hochedlinger et al took a somatic nucleus from the tail-tip of an SCID mouse-model, created through the double-knockout of the Rag-2 gene recombination-activating gene 2 , and rescued the genetic defect through the insertion of two copies of the Rag-2 gene by homologous recombination However, mature T lymphocytes were not observed, suspected to be due to selective differentiation of the transplanted stem cells into myeloid cells bone marrow precursors instead Although more work needs to be done to elucidate the pathways leading to preferential differentiation in vivo, the combination of gene therapy for the rescue of a loss of function and therapeutic cloning to bypass graft rejection holds the potential to eventually cure other immune disorders. Oncogenic activation following transduction constitutes a major drawback to this approach. In , the insertion of the transgene to treat X-linked SCID in the LMO2 oncogene caused the onset of leukemia in two out of seven patients recently treated Repeated graft rejection, even when derived through SCNT, remains an unsolved problem in the case of autoimmune disorders such as pernicious anemia and multiple sclerosis. For instance, although therapeutic cloning is not completely banned in the United States, federal funding is not permitted to be used in experiments involving the 20 cell lines in the NIH National Institute of Health registry 44 derived before August 9, Out of these cell lines approved by Bush, 12 died and the remaining is not useful for research purposes. Researchers have to therefore rely on the scarcity of private funding, although 4 American states, including California with a yearly investment of millions, have a budget allowed specifically for stem cell research Currently, due to low SCNT efficiency, it is estimated that human oocytes 35 would be needed in order to derive one observe patient-specific ntESC line. The Human Fertility and Embryo Authority, in England, allows women in fertility clinics to offer two oocytes for scientific research, provided that at least twelve oocytes are collected 25 , although the extra oocytes taken are more likely to be donated for in vitro insemination. Substantial financial gain would incite poorer women to surrender of part of a finite supply of gametes, in addition to the risks incurred through surgerical removal of the oocytes and hormonal treatments. Ovarian hyperstimulation syndrome OHSS results, in most cases, from the administration of drugs such as gonadotropin-releasing hormone agonists 27 , to induce the simultaneous maturation of multiple follicles into oocytes. Fertility clinics are the major source of human oocytes for research. The aged oocytes that did not fertilize during in vitro trials are not optimal for SCNT, as investigated by Hall et al, who observed overexpression of genes encoding for meiotic spindles proteins and a lower cleavage efficiency 30 of aged oocytes versus fresh ones. After two years of debate, Harvard is the only group currently allowed to use oocytes collected for the sole purpose of research, with informed consent. Eggan and Melton intend to generate human ntESC lines from patients with diabetes, sickle cell anemia and amyotrophic lateral sclerosis ALS , a progressive neurodegenerative condition targeting motor neurons Possible solutions to the oocyte shortage for therapeutic cloning Interestingly, SCNT could provide a solution to low human oocyte availability and a promising therapeutic approach to circumvent infertility. As reported by Nagy and

Chang, artificial gametes 32 can be created by haploidization, through SCNT into an enucleated oocyte ready to undergo meiosis upon induction. Tesarik et al incorporated the nucleus of a human cumulus cell into an enucleated allogenic oocyte. However, abnormal chromosomal segregation and mitotic spindle assembly, as observed in mice, need to be resolved before haploidization through SCNT can be safely wide-spread in fertility clinics. Once the molecular pathways of oocyte maturation are resolved, immature follicles could be collected postmortem 39 and induced to mature in vitro for research purpose. However, this option needs to be rigorously regulated, and is likely to stir an ethical controversy. An alternative to low human oocyte availability would be to use an oocyte of a different species. Successful trials were done to generate blastocysts in vitro through the SCNT of skin fibroblast nucleus from different mammals ungulates, rodents, pigs, monkey 34 and human into an enucleated bovine oocyte. The insertion of human nuclear genome into an animal oocyte, especially through electrofusion where both human and animal mitochondrial DNA coexist in the same ooplasm, raise objections among the detractors of therapeutic cloning, although the percentage of total residual animal DNA nuclear and mitochondrial is too low to consider the hybrid as a chimera. Mitochondrial heteroplasmy Immune rejection of the ntESC in cell replacement therapy is due to mitochondrial heteroplasmy as a consequence of SCNT since the nuclear donor and ooplasmic host cells are not autologous in most cases. Mitochondrial heteroplasmy is also a major cause of SCNT embryo inviability beyond the eight-cell stage because the mitochondrial-nucleus interactions necessary for the production of most mitochondrial proteins are disrupted due to inter-species incompatibility Also, antigens such as Mta are encoded by the mitochondrial genome and trigger an autoimmune response targeting the hybrid 36 after transplantation. Inter-species incompatibility can be circumvented to a certain degree if the donor and host species are closely related. For instance, embryonic cells derived from the injection of a human nucleus in a chimpanzee ooplasm were viable, contrarily to when SCNT was done with the ooplasm of a nonhuman primate such as the orangutan The transfer of mitochondria isolated from patient-specific biopsies 39 might circumvent the immune rejection problem due to mitochondrial heteroplasmy, and a female patient could in theory donate both the somatic nucleus and oocyte necessary for cell replacement therapy in her own body. The latter option offers great promises since recent studies in bovine showed that autologous SCNT embryonic production was more efficient than when the nuclear donor and ooplasmic host are from allogenic origins, and epigenetic reprogramming occurs to a significantly less extend in autologous SCNT embryos Transfer of animal contaminants The interspecies transmission of pathogens is a nonnegligible issue when injecting a human nucleus into the oocyte of another species, such as bovine or pig For instance, the porcine endogenous retrovirus PERV , although inoffensive in pigs, disrupts the transcription initiation of genes in humans, as demonstrated in vitro by Moalic et al, by integrating within the CpG islands of promoters Gene therapy approaches are being designed to reduce the infectivity of PERV due to the mannose-rich N-glycan integrated in the viral capsule Thus, through the insertion of genes such as ManIb and ManII, encoding mannosidases involved in N-glycan catabolism, the infectivity of PERV was significantly reduced but not annihilated in human cells. Animal serum and non-proliferative mouse fibroblast used as feeder-cell layer to direct the development of the human ntESC 44 is problematic since animal contaminants can be transferred to the ntESC which in turn might trigger an immune response post-transplantation, thereby revoking the goal of therapeutic cloning. N-glycolylneuraminic acid Neu5Gc is a mammalian sialic acid a sugar with acidic side-chains present in the membrane of all cells not found in humans, although most of us have anti-Neu5Gc antibodies. When human ntESC are grown on animal feeder cells or in contact with animal-derived serum, the stem cells incorporate enough Neu5Gc to potentially elicit an immune response 45 in vivo, hence killing the transplanted cells. Although the murine leukemia virus is not pathogenic 44 when transmitted from mouse feeder cells to human ntESC, non-cellular matrices are being designed to counteract the problem of animal contaminants. Neu5Gc was not reported in the cell lines cultured on this human matrix. In sum, the issue of pathogenic transmission is in the process of being solved, bringing one step further the potential for clinical application of therapeutic cloning in cell replacement therapy.

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Chapter 6 : What are Stem Cells? Types of Stem Cell and their Uses

Cancer stem cell. Cancer stem cells (CSCs) are a rare subset of cancer cells which have features such as the ability to self-renew, differentiate into defined progenies, and initiate and sustain tumor growth in vivo.

Most cells in the body are differentiated cells. These cells can only serve a specific purpose in a particular organ. For example, red blood cells are specifically designed to carry oxygen through the blood. All humans start out as only one cell. This cell is called a zygote, or a fertilized egg. The zygote divides into two cells, then four cells, and so on. Eventually, the cells begin to differentiate, taking on a certain function in a part of the body. This process is called differentiation. They have the ability to divide and make an indefinite number of copies of themselves. Other cells in the body can only replicate a limited number of times before they begin to break down. When a stem cell divides, it can either remain a stem cell or turn into a differentiated cell, such as a muscle cell or a red blood cell. Since stem cells have the ability to turn into various other types of cells, scientists believe that they can be useful for treating and understanding diseases. According to the Mayo Clinic , stem cells can be used to: Embryonic stem cells Embryonic stem cells come from human embryos that are three to five days old. They are harvested during a process called in-vitro fertilization. This involves fertilizing an embryo in a laboratory instead of inside the female body. Embryonic stem cells are known as pluripotent stem cells. These cells can give rise to virtually any other type of cell in the body. Non-embryonic adult stem cells Adult stem cells have a misleading name, because they are also found in infants and children. These stem cells come from developed organs and tissues in the body. For example, hematopoietic stem cells are a type of adult stem cell found in bone marrow. They make new red blood cells, white blood cells, and other types of blood cells. Doctors have been performing stem cell transplants, also known as bone marrow transplants, for decades using hematopoietic stem cells in order to treat certain types of cancer. Induced pluripotent stem cells iPSCs Scientists have recently discovered how to turn adult stem cells into pluripotent stem cells. These new types of cells are called induced pluripotent stem cells iPSCs. They can differentiate into all types of specialized cells in the body. This means they can potentially produce new cells for any organ or tissue. To create iPSCs, scientists genetically reprogram the adult stem cells so they behave like embryonic stem cells. This may make them more useful in understanding how diseases develop. This will help prevent the immune system from rejecting an organ transplant. Research is underway to find ways to produce iPSCs safely. Cord blood stem cells and amniotic fluid stem cells Cord blood stem cells are harvested from the umbilical cord after childbirth. They can be frozen in cell banks for use in the future. These cells have been successfully used to treat children with blood cancers, such as leukemia, and certain genetic blood disorders. Stem cells have also been found in amniotic fluid. However, more research is needed to help understand the potential uses of amniotic fluid stem cells. However, in recent years, there has been controversy surrounding the way human embryonic stem cells are obtained. During the process of harvesting embryotic stem cells, the embryo is destroyed. This raises ethical concerns for people who believe that the destruction of a fertilized embryo is morally wrong. Opponents believe that an embryo is a living human being. They argue that the embryo should have the same rights as every other human and that these rights should be protected. Supporters of stem cell research, on the other hand, believe that the embryos are not yet humans. They note that researchers receive consent from the donor couple whose eggs and sperm were used to create the embryo. Supporters also argue that the fertilized eggs created during in-vitro fertilization would be discarded anyway, so they might be put to better use for scientific research. With the breakthrough discovery of iPSCs, there may be less of a need for human embryos in research. This may help ease the concerns of those who are against using embryos for medical research. However, if iPSCs have the potential to develop into a human embryo, researchers could theoretically create a clone of the donor. This presents another ethical issue to take into consideration. Many countries already have legislation in place that effectively bans human cloning. Federal regulations on stem cell research In the United States, federal policy regarding stem cell research has evolved

over time as different presidents have taken office. Rather, regulations have placed restrictions on public funding and use. However, certain states have placed bans on the creation or destruction of human embryos for medical research. Stem cell policy under former President George W. Bush approved a law that would provide federal funding for limited research on embryonic stem cells. However, such research had to fit the following criteria: The harvesting process, which includes the destruction of the embryo, was started before 9 p. The stem cells were obtained from an embryo that was created for reproductive purposes and was no longer needed. The order removed the restrictions on federal funding for stem cell research. The NIH then published guidelines to establish the policy under which it would fund research. The guidelines were written to help make sure that all NIH-funded research on human stem cells is morally responsible and scientifically relevant. Stem cell research is ongoing at universities, research institutions, and hospitals around the world. Researchers are currently focusing on finding ways to control how stem cells turn into other types of cells. The process of cell differentiation A primary goal of research on embryonic stem cells is to learn how undifferentiated stem cells turn into differentiated stem cells that form specific tissues and organs. Researchers are also interested in figuring out how to control this process of differentiation. Over the years, scientists have developed methods to manipulate the stem cell process to create a particular cell type. This process is called directed differentiation. A recent study also discovered the first steps in how stem cells transform into brain cells and other types of cells. More research on this topic is ongoing. Cell-based therapies If researchers can find a reliable way to direct the differentiation of embryonic stem cells, they may be able to use the cells to treat certain diseases. For example, by directing the embryonic stem cells to turn into insulin-producing cells, they may be able to transplant the cells into people with type 1 diabetes. Other medical conditions that may potentially be treated with embryonic stem cells include:

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Chapter 7 : Study: Radiation Therapy Can Make Cancers 30x More Malignant

The haploid stem cells may yield new genetic screening tools and therapies. VIDEO: racedaydvl.com JcegNfB9ZPo Scientists from The Hebrew University of Jerusalem, Columbia University Medical Center (CUMC) and The New York Stem Cell Foundation Research Institute (NYSCF) have succeeded in generating a new type of embryonic stem cell that carries a single copy of the human genome, instead of.

Sign up now Stem cells: What they are and what they do Stem cells and derived products offer great promise for new medical treatments. Learn about stem cell types, current and possible uses, ethical issues, and the state of research and practice. Here are some answers to frequently asked questions about stem cells. What are stem cells? Under the right conditions in the body or a laboratory, stem cells divide to form more cells called daughter cells. These daughter cells either become new stem cells self-renewal or become specialized cells differentiation with a more specific function, such as blood cells, brain cells, heart muscle cells or bone cells. No other cell in the body has the natural ability to generate new cell types. Why is there such an interest in stem cells? Researchers and doctors hope stem cell studies can help to: Increase understanding of how diseases occur. By watching stem cells mature into cells in bones, heart muscle, nerves, and other organs and tissue, researchers and doctors may better understand how diseases and conditions develop. Generate healthy cells to replace diseased cells regenerative medicine. Stem cells can be guided into becoming specific cells that can be used to regenerate and repair diseased or damaged tissues in people. Stem cells may have the potential to be grown to become new tissue for use in transplant and regenerative medicine. Researchers continue to advance the knowledge on stem cells and their applications in transplant and regenerative medicine. Test new drugs for safety and effectiveness. Before using investigational drugs in people, researchers can use some types of stem cells to test the drugs for safety and quality. This type of testing will most likely first have a direct impact on drug development first for cardiac toxicity testing. New areas of study include the effectiveness of using human stem cells that have been programmed into tissue-specific cells to test new drugs. For the testing of new drugs to be accurate, the cells must be programmed to acquire properties of the type of cells targeted by the drug. Techniques to program cells into specific cells continue to be studied. For instance, nerve cells could be generated to test a new drug for a nerve disease. Tests could show whether the new drug had any effect on the cells and whether the cells were harmed. Where do stem cells come from? Researchers have discovered several sources of stem cells: These stem cells come from embryos that are three to five days old. At this stage, an embryo is called a blastocyst and has about cells. These are pluripotent ploo-RIP-uh-tunt stem cells, meaning they can divide into more stem cells or can become any type of cell in the body. This versatility allows embryonic stem cells to be used to regenerate or repair diseased tissue and organs. These stem cells are found in small numbers in most adult tissues, such as bone marrow or fat. Compared with embryonic stem cells, adult stem cells have a more limited ability to give rise to various cells of the body. Until recently, researchers thought adult stem cells could create only similar types of cells. For instance, researchers thought that stem cells residing in the bone marrow could give rise only to blood cells. However, emerging evidence suggests that adult stem cells may be able to create various types of cells. For instance, bone marrow stem cells may be able to create bone or heart muscle cells. This research has led to early-stage clinical trials to test usefulness and safety in people. For example, adult stem cells are currently being tested in people with neurological or heart disease. Adult cells altered to have properties of embryonic stem cells induced pluripotent stem cells. Scientists have successfully transformed regular adult cells into stem cells using genetic reprogramming. By altering the genes in the adult cells, researchers can reprogram the cells to act similarly to embryonic stem cells. This new technique may allow researchers to use reprogrammed cells instead of embryonic stem cells and prevent immune system rejection of the new stem cells. Researchers have been able to take regular connective tissue cells and reprogram them to become functional heart cells. In studies, animals with heart failure that were injected with new heart cells experienced improved heart function

and survival time. Researchers have discovered stem cells in amniotic fluid as well as umbilical cord blood. These stem cells also have the ability to change into specialized cells. Amniotic fluid fills the sac that surrounds and protects a developing fetus in the uterus. Researchers have identified stem cells in samples of amniotic fluid drawn from pregnant women to test for abnormalities â€" a procedure called amniocentesis. More study of amniotic fluid stem cells is needed to understand their potential. Why is there a controversy about using embryonic stem cells? Because human embryonic stem cells are extracted from human embryos, several questions and issues have been raised about the ethics of embryonic stem cell research. The National Institutes of Health created guidelines for human stem cell research in The guidelines define embryonic stem cells and how they may be used in research, and include recommendations for the donation of embryonic stem cells. Also, the guidelines state embryonic stem cells from embryos created by in vitro fertilization can be used only when the embryo is no longer needed. Where do these embryos come from? The stem cells are donated with informed consent from donors. The stem cells can live and grow in special solutions in test tubes or petri dishes in laboratories. Although research into adult stem cells is promising, adult stem cells may not be as versatile and durable as are embryonic stem cells. Adult stem cells may not be able to be manipulated to produce all cell types, which limits how adult stem cells can be used to treat diseases. Adult stem cells also are more likely to contain abnormalities due to environmental hazards, such as toxins, or from errors acquired by the cells during replication. However, researchers have found that adult stem cells are more adaptable than was first thought. What are stem cell lines and why do researchers want to use them? A stem cell line is a group of cells that all descend from a single original stem cell and are grown in a lab. Ideally, they remain free of genetic defects and continue to create more stem cells. Clusters of cells can be taken from a stem cell line and frozen for storage or shared with other researchers. What is stem cell therapy regenerative medicine and how does it work? Stem cell therapy, also known as regenerative medicine, promotes the repair response of diseased, dysfunctional or injured tissue using stem cells or their derivatives. It is the next chapter in organ transplantation and uses cells instead of donor organs, which are limited in supply. Researchers grow stem cells in a lab. These stem cells are manipulated to specialize into specific types of cells, such as heart muscle cells, blood cells or nerve cells. The specialized cells can then be implanted into a person. For example, if the person has heart disease, the cells could be injected into the heart muscle. The healthy transplanted heart muscle cells could then contribute to repairing defective heart muscle. Researchers have already shown that adult bone marrow cells guided to become heart-like cells can repair heart tissue in people, and more research is ongoing. Have stem cells already been used to treat diseases? Doctors have performed stem cell transplants, also known as bone marrow transplants. These transplants use adult stem cells or umbilical cord blood. Researchers are testing adult stem cells to treat other conditions, including a number of degenerative diseases such as heart failure. What are the potential problems with using embryonic stem cells in humans? For embryonic stem cells to be useful in people, researchers must be certain that the stem cells will differentiate into the specific cell types desired. Researchers have discovered ways to direct stem cells to become specific types of cells, such as directing embryonic stem cells to become heart cells. Research is ongoing in this area. Embryonic stem cells can also grow irregularly or specialize in different cell types spontaneously. Researchers are studying how to control the growth and differentiation of embryonic stem cells. Researchers continue to study how to avoid these possible complications. What is therapeutic cloning, and what benefits might it offer? Therapeutic cloning, also called somatic cell nuclear transfer, is a technique to create versatile stem cells independent of fertilized eggs. In this technique, the nucleus, which contains the genetic material, is removed from an unfertilized egg. The nucleus is also removed from the cell of a donor. This donor nucleus is then injected into the egg, replacing the nucleus that was removed, in a process called nuclear transfer. The egg is allowed to divide and soon forms a blastocyst. Some researchers believe that stem cells derived from therapeutic cloning may offer benefits over those from fertilized eggs because cloned cells are less likely to be rejected once transplanted back into the donor and may allow researchers to see exactly how a disease develops. Has therapeutic cloning in people been successful? However, in recent studies, researchers have

created human pluripotent stem cells by modifying the therapeutic cloning process. Researchers continue to study the potential of therapeutic cloning in people.

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Chapter 8 : Stem Cell Basics III. | racedaydvl.com

Obtain autologous blood, stem cells and/or tumor tissue from patientscurrently with cancer for laboratory analysis and ex vivo generation ofautologous anti-tumor lymphocytes for future enrollment on a Surgery Branch adoptive cell therapy clinical trial.

In healthy adult laboratory animals, progenitor cells migrate within the brain and function primarily to maintain neuron populations for olfaction the sense of smell. Pharmacological activation of endogenous neural stem cells has been reported to induce neuroprotection and behavioral recovery in adult rat models of neurological disorder. Clinical and animal studies have been conducted into the use of stem cells in cases of spinal cord injury. One pair of reports of identical baseline characteristics and final results, was presented in two publications as, respectively, a patient randomized trial and as a subject observational study. Other reports required impossible negative standard deviations in subsets of people, or contained fractional subjects, negative NYHA classes. A university investigation, closed in without reporting, was reopened in July However, the immune system is vulnerable to degradation upon the pathogenesis of disease, and because of the critical role that it plays in overall defense, its degradation is often fatal to the organism as a whole. Diseases of hematopoietic cells are diagnosed and classified via a subspecialty of pathology known as hematopathology. The specificity of the immune cells is what allows recognition of foreign antigens, causing further challenges in the treatment of immune disease. Identical matches between donor and recipient must be made for successful transplantation treatments, but matches are uncommon, even between first-degree relatives. Research using both hematopoietic adult stem cells and embryonic stem cells has provided insight into the possible mechanisms and methods of treatment for many of these ailments. In this process, HSCs are grown together with stromal cells , creating an environment that mimics the conditions of bone marrow, the natural site of red-blood-cell growth. Erythropoietin , a growth factor , is added, coaxing the stem cells to complete terminal differentiation into red blood cells. Researchers are confident that the tooth regeneration technology can be used to grow live teeth in people. In theory, stem cells taken from the patient could be coaxed in the lab turning into a tooth bud which, when implanted in the gums, will give rise to a new tooth, and would be expected to be grown in a time over three weeks. The process is similar to what happens when humans grow their original adult teeth. Many challenges remain, however, before stem cells could be a choice for the replacement of missing teeth in the future. The group, led by Sheraz Daya , was able to successfully use adult stem cells obtained from the patient, a relative, or even a cadaver. Further rounds of trials are ongoing. In theory if the beta cell is transplanted successfully, they will be able to replace malfunctioning ones in a diabetic patient. In an adult, wounded tissue is most often replaced by scar tissue , which is characterized in the skin by disorganized collagen structure, loss of hair follicles and irregular vascular structure. In the case of wounded fetal tissue, however, wounded tissue is replaced with normal tissue through the activity of stem cells. This method elicits a regenerative response more similar to fetal wound-healing than adult scar tissue formation. In , oogonial stem cells were isolated from adult mouse and human ovaries and demonstrated to be capable of forming mature oocytes. Human embryonic stem cells clinical trials Regenerative treatment models[edit] Stem cells are thought to mediate repair via five primary mechanisms: In addition, they have been found to secrete chemokines that alter the immune response and promote tolerance of the new tissue. This allows for allogeneic treatments to be performed without a high rejection risk. Researchers are able to grow up differentiated cell lines and then test new drugs on each cell type to examine possible interactions in vitro before performing in vivo studies. This is critical in the development of drugs for use in veterinary research because of the possibilities of species specific interactions. The hope is that having these cell lines available for research use will reduce the need for research animals used because effects on human tissue in vitro will provide insight not normally known before the animal testing phase. Rather than needing to harvest embryos or eggs, which are limited, the researchers can remove mesenchymal stem cells with greater ease and

greatly reducing the danger to the animal due to noninvasive techniques. This allows the limited eggs to be put to use for reproductive purposes only. Spermatogonial stem cells have been harvested from a rat and placed into a mouse host and fully mature sperm were produced with the ability to produce viable offspring. Currently research is underway to find suitable hosts for the introduction of donor spermatogonial stem cells. If this becomes a viable option for conservationists, sperm can be produced from high genetic quality individuals who die before reaching sexual maturity, preserving a line that would otherwise be lost. Accordingly, stem cells derived from bone marrow aspirates, for instance, are cultured in specialized laboratories for expansion to millions of cells. Research is underway to examine the differentiating capabilities of stem cells found in the umbilical cord, yolk sac and placenta of different animals. These stem cells are thought to have more differentiating ability than their adult counterparts, including the ability to more readily form tissues of endodermal and ectodermal origin. Stem-cell controversy There is widespread controversy over the use of human embryonic stem cells. This controversy primarily targets the techniques used to derive new embryonic stem cell lines , which often requires the destruction of the blastocyst. Opposition to the use of human embryonic stem cells in research is often based on philosophical, moral, or religious objections. On 23 January , the US Food and Drug Administration gave clearance to Geron Corporation for the initiation of the first clinical trial of an embryonic stem-cell-based therapy on humans. The trial aimed evaluate the drug GRNOPC1, embryonic stem cell -derived oligodendrocyte progenitor cells, on people with acute spinal cord injury. The trial was discontinued in November so that the company could focus on therapies in the "current environment of capital scarcity and uncertain economic conditions". Various clinical trials on MSCs have failed which used cryopreserved product immediately post thaw as compared to those clinical trials which used fresh MSCs. Misaligned breaks due to severe trauma, as well as treatments like tumor resections of bone cancer, are prone to improper healing if left to the natural process alone. Scaffolds composed of natural and artificial components are seeded with mesenchymal stem cells and placed in the defect. Within four weeks of placing the scaffold, newly formed bone begins to integrate with the old bone and within 32 weeks, full union is achieved. Stem cells have been used to treat degenerative bone diseases. The normally recommended treatment for dogs that have Leggâ€”Calveâ€”Perthes disease is to remove the head of the femur after the degeneration has progressed. Recently, mesenchymal stem cells have been injected directly in to the head of the femur, with success not only in bone regeneration, but also in pain reduction. This is important interest for those with reduced healing capabilities, like diabetics and those undergoing chemotherapy. These cells were injected directly into the wounds. Within a week, full re-epithelialization of the wounds had occurred, compared to minor re-epithelialization in the control wounds. This showed the capabilities of mesenchymal stem cells in the repair of epidermal tissues. These are often not found until after they have become worse because of the difficulty in visualizing the entire soft palate. This lack of visualization is thought to also contribute to the low success rate in surgical intervention to repair the defect. As a result, the horse often has to be euthanized. Recently, the use of mesenchymal stem cells has been added to the conventional treatments. After the surgeon has sutured the palate closed, autologous mesenchymal cells are injected into the soft palate. The stem cells were found to be integrated into the healing tissue especially along the border with the old tissue. There was also a large reduction in the number of inflammatory cells present, which is thought to aid in the healing process. Autologous stem cell based treatments for tendon injury, ligament injury, and osteoarthritis in dogs have been available to veterinarians in the United States since Over privately owned horses and dogs have been treated with autologous adipose-derived stem cells. The efficacy of these treatments has been shown in double-blind clinical trials for dogs with osteoarthritis of the hip and elbow and horses with tendon damage. Conventional therapies are very unsuccessful in returning the horse to full functioning potential. Natural healing, guided by the conventional treatments, leads to the formation of fibrous scar tissue that reduces flexibility and full joint movement. Traditional treatments prevented a large number of horses from returning to full activity and also have a high incidence of re-injury due to the stiff nature of the scarred tendon. Introduction of both bone marrow and adipose derived stem cells, along with natural

mechanical stimulus promoted the regeneration of tendon tissue. The natural movement promoted the alignment of the new fibers and tendocytes with the natural alignment found in uninjured tendons. Stem cell treatment not only allowed more horses to return to full duty and also greatly reduced the re-injury rate over a three-year period. The embryonic stem cells were shown to have a better survival rate in the tendon as well as better migrating capabilities to reach all areas of damaged tendon. The overall repair quality was also higher, with better tendon architecture and collagen formed. There was also no tumor formation seen during the three-month experimental period. Long-term studies need to be carried out to examine the long-term efficacy and risks associated with the use of embryonic stem cells. Horses and dogs are most frequently affected by arthritis. Natural cartilage regeneration is very limited and no current drug therapies are curative, but rather look to reduce the symptoms associated with the degeneration. Different types of mesenchymal stem cells and other additives are still being researched to find the best type of cell and method for long-term treatment. There has been a lot of success recently injecting mesenchymal stem cells directly into the joint. This is a recently developed, non-invasive technique developed for easier clinical use. Dogs receiving this treatment showed greater flexibility in their joints and less pain. Adipose and bone marrow derived stem cells were removed and induced to a cardiac cell fate before being injected into the heart. The heart was found to have improved contractility and a reduction in the damaged area four weeks after the stem cells were applied. Tissue was regenerated and the patch was well incorporated into the heart tissue. This is thought to be due, in part, to improved angiogenesis and reduction of inflammation. Although cardiomyocytes were produced from the mesenchymal stem cells, they did not appear to be contractile. Other treatments that induced a cardiac fate in the cells before transplanting had greater success at creating contractile heart tissue. These cells involved in the secondary damage response secrete factors that promote scar formation and inhibit cellular regeneration. Mesenchymal stem cells that are induced to a neural cell fate are loaded onto a porous scaffold and are then implanted at the site of injury. The cells and scaffold secrete factors that counteract those secreted by scar forming cells and promote neural regeneration. Eight weeks later, dogs treated with stem cells showed immense improvement over those treated with conventional therapies. Dogs treated with stem cells were able to occasionally support their own weight, which has not been seen in dogs undergoing conventional therapies. Peripheral nerves are more likely to be damaged, but the effects of the damage are not as widespread as seen in injuries to the spinal cord. Treatments are currently in clinical trials to repair severed nerves, with early success. Stem cells induced to a neural fate injected in to a severed nerve. Within four weeks, regeneration of previously damaged stem cells and completely formed nerve bundles were observed. Hematopoietic stem cells have been used to treat corneal ulcers of different origin of several horses. These ulcers were resistant to conventional treatments available, but quickly responded positively to the stem cell treatment. Stem cells were also able to restore sight in one eye of a horse with retinal detachment, allowing the horse to return to daily activities.

Chapter 9 : Stem cells: What they are and what they do - Mayo Clinic

The most deadly cell type within a tumor or blood cancer, known as cancer stem cells (CSCs), has the ability to give rise to all the cell types found within that cancer.