Regeneration Biology
Rajesh Ramachandran
Department of Biological Sciences
IISER Mohali
Week: 9
Lecture: 45

W9L45_Ethics of stem cell research in regeneration studies, regenerative medicine and biotechnology

Hello everyone, welcome back to another class on regenerative biology. Today's topic, as you can see here, is about the ethics of stem cell research in regeneration studies, regenerative medicine, and biotechnology. This topic may sound a little dry, with not too much pictorial detail, etc., but As we go through each topic's content, you will understand how important it is to take care of or be concerned about ethics. Let us think about what the ethical aspects of stem cell research are. Recent findings in stem cell research and biotechnology, particularly concerning sources beyond embryonic stem cells, are reshaping the ethical landscape and moving towards a more nuanced understanding of natural stem cell therapies.

For example, beyond embryonic stem cells, what angles should we consider regarding traditional ethical concerns primarily focused on embryonic stem cells due to their potential for creating human life, the moral implications of destroying embryos for research, and their applications? This is the primary ethical concern in the sense that... Embryonic stem cell research is being promoted.

People will keep making embryos or aborting human embryos, and it will be like a business. So, this is one ethical concern. So you have no right to kill a human embryo. That is one angle. But then alternative sources have come.

What are they? Research has identified stem cells in various other sources, such as adult tissues like bone marrow, blood, amniotic fluid, and umbilical cord blood, as well as the techniques to reprogram adult cells, namely induced pluripotent cells, etc. have come into the picture. So now the so-called embryonic stem cell that angles at the so-called ethical angle is kind of diluted, and then certain other angles have come forward that are natural stem cell therapies. The concept of natural stem cell therapy arises from the observation that the body naturally utilizes stem cells for repair and regeneration, particularly in rapidly dividing tissues like blood cells. Now the question is, which situations we will discuss.

So one angle is that you are using stem cells from some source, say a known-source, an

unknown source, or the patient-derived source, and you are manipulating them and putting them into the patient; the patient is benefiting. That is one aspect of stem cell therapy. Then one can ask, did you unnecessarily make an unfit person fit? and allowed him to survive another, gave him chances. This is against natural selection. This is one ethical perspective.

The second thing is that stem cells should be used only for research purposes, not for changing the life landscape of a person. So these are another ethical angle. When it comes to natural stem cell therapy, without the intervention of a clinician, doctor, or anyone else, the naturally occurring stem cells, not adult stem cells, originate from some other source. We will discuss that. And that contributed, but if that stem cell doesn't belong to that patient, then how does this come into the picture? So those are the angles we have to discuss.

So if you look further, the ethical considerations with alternative sources, examples of alternate sources of stem cells, alternate means to embryonic stem cells, somatic stem cells, and the ethical debate surrounding the collection and use of somatic stem cells from aborted fetuses and umbilical cords are emerging. So, an aborted fetus raises the question of how the stem cells from that fetus can be useful if it is aborted for some reason. This is another question. But the fetus may have aborted not because something was wrong with the fetus, but because something was wrong with the mother. That is also why we have to think about it.

So, from one angle, a fetus may be bad; from another angle, a fetus may be good, but the mother is not good. So, there is technically nothing wrong with collecting an aborted fetus, but it can become a business. This is the angle you should explore. Induced pluripotent stem cells (iPSCs), which are derived from adult cells and reprogrammed to act like embryonic stem cells, raise questions about the potential for off-target effects and long-term safety of using altered adult cells. Because you're taking the cells, altering them, and once they become stem cells, how sure are we that the methodology used for altering them has completely disappeared? It may still have relics that epigenetic changes or whatever transcription factors are expressed as part of the alteration may linger around, and that can create a chance of getting cancer, which is also possible, and perinatal stem cells.

So, in this way, the ethical angle is that you were trying to help a patient, but in that process, you gave him a death sentence through cancer. This is the angle you should consider; if you hadn't intervened, he probably would have lived a few more years peacefully. With that organ defective, you tried fixing it through stem cells, and he ended up getting cancer. He or she is okay, so perinatal stem cells, found in amniotic fluid and

umbilical cord blood, are also being explored extensively, but their use raises questions about consent and storage. Potential future applications, etc.

, are very unclear or gray areas of research. Let us think about an overview of the ethical concerns in biotechnology and stem cell research. If you look closely, biotechnology is crucial in developing tools. Therapeutics involve modifying and engineering stem cells, which is the essence of biotechnology, allowing you to intervene and alter natural processes to suit your needs, much like how milk is made into paneer or cottage cheese, which can then be used to prepare a dish. Something this kind of transition you should think about when you are discussing how biotechnology tweaks a given cell's ethical frameworks.

When you look closely, stem cell research progresses by applying existing ethical frameworks and considering new ethical implications. It is crucial, especially regarding the clinical translation of basic stem cell knowledge into safe, effective, and acceptable patient therapies, so this is one of the major implications one should keep in mind: the ethical frameworks should not be broken under any circumstances. Let us Give some examples of the stem cell therapy hematopoietic stem cell transplantation, which is extensively done these days. This is the only FDA-approved stem cell therapy used to treat blood cancers and other conditions that can be fixed through bone marrow transplantation, which is an approved strategy. It can be from relatives or tissue-matched controls because it is a less complex tissue.

In the body. Maybe if it is an unrelated individual, you may have to be on immunosuppressants for the rest of your life, but still, it is an approved therapy. And stem cell therapies for other diseases include research that is underway to develop stem cell treatments for neurodegenerative diseases, diabetes, heart disease, and other conditions. They are also underway because stem cells can hold the key to fixing this trouble. Let us think about the ethical challenges. What are the ethical challenges that come through this informed consent, ensuring that the patients understand the risks and benefits of stem cell therapies? And it isn't easy.

You cannot tell a patient that we are fixing them, but they may end up getting cancer. No one is going to say that, okay, I don't mind getting cancer. I want this disease to be cured. Nobody will say anything. So this is one angle one has to explore and understand: a person shaking their head or nodding their head doesn't mean that they understood.

So they may sign for the sake of the consent form, but did we really make them understand? So this is another ethical question raised. You told them, okay, but did they understand? So this is something that is a gray area to define. Access and equity. Stem

cell therapies can be costly, raising concerns about equitable access to these treatments. Stem cell therapy can fix a problem.

Two people are affected now. One is a rich person; another is a poor person. Stem cell therapy is available. And a rich person, I am fixing it because he gives me money. And the poor person I am not fixing.

I am telling you, okay, you don't have the right to live because you don't have money. Because when a therapy is available and if it is a life-saving therapy, it should be open to all. Money should not come into the picture. But we all know that for any treatment, money is the concern, the factor that comes into the picture. One can ask a question: research and stem cell research are meant to help humanity, and you are not helping a poor man; rather, you are helping a rich man.

So these are all the ethical angles. Scientific rigor and transparency are essential to ensure that stem cell therapies are based on sound scientific evidence. "Sound" means strong, not. Audible sound, scientific evidence, and that clinical trials are conducted ethically and transparently; this is another angle. There are, like, those who follow hospital connections and affairs, and such things have come up in lots of movies.

Also, if a person is declared brain dead... is he genuinely brain dead or just because his tissue is a very exciting tissue which helps a man in queue to receive an organ they find that okay this youngster's organ tissue is matching and they simply he could have recovered back he was just in an unconscious state and doctors immediately declared him brain dead and took his liver or heart or whatever organ required for a rich man so these are all the things one has to Consider that whenever there is scientific progress aimed at helping humanity, equitability or equal distribution, irrespective of a person's social status, is a tough thing to achieve. Although it's an ideal to strive for, it is difficult to accomplish because often the rich get what they want.

Let us give some examples of facts about natural stem cell therapy. We have discussed natural stem cell therapy. The natural replacement of damaged cells by stem cells occurs actively and often in adult tissues, especially in rapidly dividing cells such as blood cells, which happens every day. Like your skin is peeling, your intestinal epithelium is peeling every now and then; those stem cells underneath are fixing them. An exciting case example is in Boston; however, it involves a type of natural stem cell therapy provided to a mother by her fetus.

How did it happen? Long after the fetus is born, she did not take a stem cell from the fetus and inject it into her because there is a profound lack of medical intervention. This

therapy seems to be natural enough, and this is unlikely to be morally suspect, but let us dissect how it went; nevertheless, one may feel morally uncertain about giving this type of therapy to patients who would not naturally receive it. If a mother had an issue, such as organ failure, she had the chance for stem cell therapy because of the fetus in her womb. If she was not pregnant, if she did not have this fetus in her embryo, the chances of getting stem cells into her bloodstream are minimal.

So this raises a question. Did one do justice to the fetus? But no one injected stem cells manually into the bloodstream. This is the angle you should think about. Although one promising technology involves the utilization of blighted ova, let us discuss a little more about natural stem cell therapy, as it is a case for moral evaluation. It ultimately demonstrates the importance of permissible stem cell research and therapy, and it is even absent. In an agreement about the definition of when embryonic life begins.

Does it start from an egg? Does it start from sperm? Is it starting from the zygote? Is it starting from the blastula? So these are all questions which are not defined. Although one promising technology is blighted ovum utilization, it uses fertilized but developmentally bankrupt eggs. That means it cannot give rise to an embryo. It is fertilized, but it will not give rise to an embryo. It is argued that utilizing unfertilized eggs to derive totipotent stem cells obviates the moral debate over when life begins in an embryo; however, one should also understand that ovum and sperm are released, but only one gets fertilized even in natural breeding.

How about the other sperms? How about other ova? Not that one ovum is released; one ovum gets fertilized, and in a female's lifespan, throughout the lifespan, the ova are getting wasted. Isn't it wastage of life there? So these are all some unclear areas. Two existing technologies fulfill this criterion: one is somatic cell nuclear transfer, which we discussed in the previous class, and parthenogenic stem cell derivation if you made stem cells from a parthenogenic source. A parthenogenic individual is a form of vegetative propagation, so we can technically call it my clone, only my extension, or something like that. One can argue that somatic cell nuclear transfer means I did not take the embryo; I just took a nucleus from one donor and put it into the.

.. Ovum and I made it to start dividing, so I created the embryo, but still, one can ask why that embryo cannot make an independent life. It's almost like saying if there are monozygotic twins, two are there; oh, one is affordable, one we can kill because in normal birth only one is formed. So now, two are independent; the other one can be used for whatever you want. That logic doesn't help because these are all the angles one should keep in mind, although these technologies are far from therapeutic yet. Concerns over the morality of embryonic stem cell derivation should not hinder its advancement.

Means whether you use it or not, you cannot say that it should not be there. It's just like, you know, some governments acquire lots of weapons and lots of strategic weapons, but they have no plan to attack any country. So if you have no plan of attacking any country, can you have, or cannot have? So, this is a debatable question. One can ask, then why do you need a weapon? You have no plan for attacking. Then another argument says, "No, we want to safeguard ourselves.

" Then the question asked is if you want to safeguard yourself; if you have no plan of using it, how does it provide protection? So the idea is that if you have weapons, it automatically secures you, not uses your policy. So these are all the angles that, when you make an embryo, you either allow it to become independent or you allow it to divide at a certain stage and then use it. So, these are all the questions one should have. Let us go into detail about a case study. A 37-year-old mother of three kids comes into the clinic presenting with abdominal pain, marked tiredness, and puffy ankles.

The standard array of diagnostic tests suggests acute liver failure. Your patient rejects all treatment options, including radical liver transplant surgery. Patients don't want. And decides to wait and see how her disease stage progresses. Now comes the interesting part: remarkably, perhaps miraculously, six months later she shows signs of a complete recovery from this liver problem, which according to doctors needed a surgical intervention or a transplantation.

Despite a lack of medical intervention—that is, no medical intervention—it recovered. Just over a year ago, researchers at the New England Medical Center in Boston presented new data on this scenario involving an old cell type, pregnancy-associated progenitor cells, known as PAPC, which might explain the patient's Deus Ex Machina recovery. What does it mean when miraculous recovery is called; it's a Latin word for recovery. As far back as 1979, people used to believe that it was shown that women who gave birth to sons retain some of the son's fetal cells, for example, PAPCs, which can in turn give rise to multiple cell types along the hematopoietic stem cell pathway to differentiation.

But it need not be a son; it can also be daughters. It has to be a fetus. After all, the reasoning goes that the placental blood barrier is not a perfectly selective portal. And some fetal blood and cells will cross into the maternal circulation. And since it is 50% maternal, the tissue rejections will be minimal.

And if it is rejected, it will not stay. But if the tissue matching is perfect, the fetus-derived stem cells will circulate in the mother. How long? Up to 27 years old. What is surprising, however, is the ubiquity and persistence of these fetal stem cells. They can be

found in maternal circulation for up to 27 years after the baby is born. Until then, if the mother is facing some trouble, it can get.

This doesn't mean that if a mother gave birth for an extra 27 years, she won't get a liver complaint. It depends on how much stem cell leakage occurred, how those stem cells continue to divide, how they were not rejected by her immune system, etc. These fetal stem cells were found to localize in diseased organs and repopulate them. For example, in one woman with a thyroid adenoma, a biopsy revealed two populations of cells. Her germline cancerous thyroid cells were surrounded by healthy thyroid cells derived from her son's fetus.

Son, right now she is not pregnant, but she saw her own damaged cancerous cell, and it is surrounded by the fetal cells. Even more strikingly, one woman with liver disease had significant repopulation of her liver with healthy fetal-derived hepatocytes, the first indication of a functional non-hematopoietic stem cell-derived PAPC. Now you bring in your ethical angle. You took embryonic stem cells from your own fetus without his or her permission and injected them into your bloodstream.

Is it ethically right? Mother should have been dead. So one can argue from this angle. Whatever the mechanism involved, the idea of fetal cells expressing non-hematopoietic markers is novel and may have important long-term health implications, in this case, benefits for the woman who has undergone pregnancy by providing her with a younger population of cells that may have different capabilities in response to tissue injury. Just because the mother conceived, she is getting an added lease on life because her organs could have been damaged due to old age; now she has a fresh stock of cells. Fetus-derived stem cell. The fertilization itself may occur not in the body but in a test tube.

All of you would have heard about test-tube babies. It is estimated that currently in the United States alone, around 400,000, or 4 lakh. Frozen embryos left over from in vitro fertilization treatments can be used as a source of embryonic stem cells. If this is true, one can happily make tissue-matching stem cells because they are frozen and are never going to be inoculated since those parents have already used them. They take multiple eggs and multiple sperm, fertilize them, and create multiple embryos, but no one who seeks child care or wants to have a child through artificial insemination or other methods wants a dozen children.

They want one child or maybe two children. What about the rest of the eggs and sperm? They freeze it and keep it. So they are still there. Are these fetal stem cells that have our patient's liver embryonic or adult-derived? Now, when this kind of situation is present, is it yours, or does your liver belong to you, or does your liver belong to your fetus, or your

son or daughter? What you.

.. gave birth to. Fetal stem cells that transfer across the placenta and remain in utero for decades have been identified as adult hematopoietic stem cells. Because the hematopoietic stem cells cannot typically transdifferentiate into epithelial cells such as hepatocytes, the circulating stem cells in our patient are likely of embryonic origin. because of which they are able to give rise to the damaged tissue or the differentiation, if possible, because hematopoietic stem cells normally don't do that. What seems more important then is the potential moral objection to harvesting embryos for stem cell research and therapy. It is less contentious to harvest embryos, often dozens at a time, for assisted reproduction, which is normally done.

The sheer number of leftover embryos in thousands of fertilization clinics across the United States, one example country because that country has all the records of this, other countries will also have, is a testament to the moral acceptability of the technology. What is the fate of these 400,000 frozen embryos? Are they going to become human? Are they going to be discarded? What is the purpose of keeping them? A few more ethical considerations are needed. Those who have no moral qualms against such assisted reproductive technology may nevertheless oppose using these frozen embryos to derive embryonic stem cells for research purposes. One can always say one husband and one wife are not having normal fertilization, which is why they are not having kids, but doctors will intervene. They will take the egg from the mother and sperm from the father, fertilize them, and implant them into the mother or a surrogate mother.

It is perfectly fine, and that is allowed. You won't say that, okay, it is your fate; you shouldn't have kids, but that is assisted using spare eggs and spare sperm. The ethical question comes into the picture. One distinction that these opponents make is the seeming unnaturalness of stem cell research. They argue that the only natural way to give moral weight to the lives of frozen embryos is to implant them and carry the fetus through a full pregnancy, which normally no one will do. In vitro fertilization, it is argued, is merely assistance with reproduction, a natural phenomenon in which all healthy humans may usually engage.

Implanting a fertilized embryo back into a mother's womb is analogous to using a respirator to assist breathing or implanting a pacemaker to control cardiac arrhythmia in a patient. Using a fertilized embryo for scientific research disregards the natural order of things, disrespecting the sanctity of the embryo itself. So these are all the points to consider. The argument of such naturalness, the so-called "in quote," is an old one: forces larger than human beings shape the external world, a higher order with which we are not to meddle. However, using naturalness as a proxy for morality fails when we consider

other highly accepted medical procedures.

Very basically, perhaps we keep a patient on life support despite his natural tendency to die. We don't let them die. So, because our morality supports it, our morality doesn't allow taking embryonic stem cells and putting them through these frozen embryos. The pacemaker we installed creates an artificial, not a natural rhythm in the heart. We sometimes induce childbirth as early as 32 weeks if the mother's life is in danger.

If we feel that the baby's health would suffer or the mother's health would suffer during a prolonged pregnancy. Indeed, in vitro fertilization itself is hardly natural in that it eliminates conception from the natural reproduction process. It seems that all advances in medical technology to do something unnatural to alleviate pain and suffering or to offer the joys of various natural procedures like childbearing intend to further natural life, which seems a more appropriate standard than naturalness. So these are all tough areas to dissect. Moreover, regaining the ability to walk after suffering from a spinal cord injury or seeing light after several years of retinal degeneration enhances the benefits of stem cell therapy.

Surely, it is the same, on a scale of naturalness, as childbearing, to which these critics do not seem to object. So failure to signal the mother that the development is progressing within normal limits results in spontaneous maternal reversion to a non-pregnant state with the expulsion of the failed concept. The concept of such mechanisms to ensure the robustness of offspring is probably as important to the species' survival as the capacity for reproduction itself.

Nature celebrates success and designs failures. This is what we always see. An inability to develop into a healthy offspring does not, however, necessarily negate the potential of a fertilized egg to give rise to stem cells. That should be allowed. Thus, many eggs traditionally doomed to die during embryogenesis could be utilized for stem cell production. So this notion highlights the urgent need to be able to distinguish developmentally capable fertilized eggs from unacceptable fertilized eggs.

So every oak tree was once a seed. It does not follow that accounts are oak trees or that I should treat the loss of an account eaten by a squirrel in my front yard as some kind of loss like the death of the oak tree caused by a storm. Despite their developmental continuity, acorns and oak trees are different. So are human embryos and human beings. So we will learn more about embryonic stem cells and regenerative biology in the next class. Thank you.