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Tissue-Engineered Trachea Transplantation

### FOCUS ON FUTURE MEDICINE - TISSUE ENGINEERED TRACHEA TRANSPLANTATION

Every New Year we looked to the future and dream of what is possible. ReachMD radio is proud to present our special series, Focus on Future Medicine.

An international team of scientist from Spain, Italy and UK recently developed a method of engineering a trachea from a patient's own stem cells. The trachea was then successfully transplanted to the patient. What implications does this stem cell technique have for other organ transplants? You are listening to ReachMD, The Channel for Medical Professionals. Welcome to The Clinician's Roundtable. I am your host Dr. Lee Freedman and joining us to discuss tissue engineered trachea transplantation is Dr. Paolo Macchiarini, Head Of Thoracic Surgery at the Hospital Clinic in Barcelona, Spain. Dr. Macchiarini performed this successful trachea transplant.

#### DR. LEE FREEDMAN:

Thank you for being with us Dr. Macchiarini.

#### DR. PAOLO MACCHIARINI:

Thank you for the invitation.

#### DR. LEE FREEDMAN:

Please tell us with this patient. Why did this patient need a transplant and why was this person a candidate for this special procedure?

#### DR. PAOLO MACCHIARINI:

Well, this is a 30 years' old lady that I saw for the first time almost three-half years ago. By that time, she suffered from airway tuberculosis. After medical treatment, she had as a consequence of this medical tuberculosis, stenosis and narrowing of the airway at 2 levels, one at the subglottic level just below the larynx and the second on her left main bronchus. We treated surgically the upper stenosis at subglottic level and put the stent inside the left main bronchus because we thought that by that time, a surgery in this particular side would be very dangerous. Unfortunately, she did not tolerate well or lets say at all, this stent placement, required multiple hospitalizations, interventions like mobilization, toilets and so forth. Hence we decided 6 months later to take off the stent. Unfortunately, we did not have any other therapies, so we just were waiting and gaining time because on the animal lab, we were actively investigating the possibility to transplant tracheas with the tissue engineering processes and therefore eventually to go far in these investigations, so that we could help that patients. It happens that she remained stable almost 2 years, but by the end of 2007 she was worsening and in

January she presented with a really poor critical status, shortness of breath, relapsing pneumonias and we had only 2 therapies, which was one first take off the lung and do that plastically, really very complicated surgery at the airway bifurcation or try the tissue trachea transplant. Because she was so young, we felt that probably the best will be to do the transplant because we had very preliminary, but very convincing evidence that at least in peaks, this would work. We presented just before the result at the Medical Association of Thoracic Surgery meeting and we are very confident about that. We talked to her saying that well just before taking off the lung, why we do not try? If it works, then we are all very, very happy because we just replaced your bronchus with another trachea with but with your own stem cells, so you do not need the immunosuppressive drugs. This was at least what we had in the lab.

**DR. LEE FREEDMAN:**

Was it considered, is it done to use cadaver trachea transplantation or animal or other types of transplantation material other than growing out of person's own stem cells?

**DR. PAOLO MACCHIARINI:**

In this particular case, we just took a cadaveric human trachea donated here in Spain from a lady. We processed that trachea in the way that we took off the cells and the major histocompatibility complex antigens class 1 and 2 and once this trachea was completely decellularized, we used it on one side of the patient's own respiratory cells and to the stem cells, which were after that differentiated in chondrocytes to recede completely this foreign trachea with autologous or own cells of the patient.

**DR. LEE FREEDMAN:**

That's fascinating. So it was a cadaver trachea, but then you had to treat it, so that all of its antigenic properties were stripped?

**DR. PAOLO MACCHIARINI:**

Exactly.

**DR. LEE FREEDMAN:**

And then her own stem cells were used to kind of cement this in place along with some of her respiratory epithelium.

**DR. PAOLO MACCHIARINI:**

Exactly. The stem cells were put on the external surface and the respiratory cells on the internal surface, so we passed from having a dead trachea to a living trachea, which was made by the donated trachea in the living cells from the own patient.

**DR. LEE FREEDMAN:**

That is fascinating and in terms of using the stem cells, you did say they were somewhat differentiated?

**DR. PAOLO MACCHIARINI:**

Well, yes, because we did a bone marrow aspiration and then we put this obtained stem cells in culture and the first step was to expand

them because we did not have that much or that many cells. We needed millions and millions cells to produce the chondrocytes. So this undifferentiated cells were then stimulated to differentiate into chondrocytes. The specific cells that just lie on the external surface of the trachea and this took at least one-half month to get this process done.

**DR. LEE FREEDMAN:**

Are there specific ways? There must be that you can take a stem cell and have it differentiate along particular cell lines.

**DR. PAOLO MACCHIARINI:**

Oh, yes. For instance in this specific case it was made by stimulating them through the specific growth factors, the parathyroid hormone growth factors in the same way as for instance you could stimulate the outer stem cells to differentiate in endothelial cells using other types of growth factors. So the growth factors were used to give these adult cells the signal to differentiate them into specific cells that we wanted to have.

**DR. LEE FREEDMAN:**

If you are just tuning in, you are listening to The Clinician's Roundtable on ReachMD, The Channel For Medical Professionals. I am your host Dr. Lee Freedman and joining me to discuss tissue engineered trachea transplantation is Dr. Paolo Macchiarini, Head Of Thoracic Surgery at the Hospital Clinic in Barcelona, Spain.

Dr. Macchiarini, you said that the whole procedure took about 90 days.

**DR. PAOLO MACCHIARINI:**

Or lets say the entire procedure took 3 months. From the very beginning where we had a chance to have donated human trachea up to the seeding process of the autologous cells with this trachea, so more or less 3 months. Yes.

**DR. LEE FREEDMAN:**

Interesting and how has the patient done subsequent to the procedure.

**DR. PAOLO MACCHIARINI:**

The patient went home 10 days after surgery and she had 3 checks during the subsequent month and she is now enjoying her life in Colombia.

**DR. LEE FREEDMAN:**

That is incredible and so far no recurrent pneumonias or other respiratory issues?

**DR. PAOLO MACCHIARINI:**

Her lung is still recovering because clearly her lung was damaged because of these resistance obstacle at the level of the left main bronchus and this is the reason why now and then she has some problems with the lung, but the episodes are by far less and she is doing really very fine. For instance, we checked the endoscopic view and the antibodies panel in her blood to see whether or not there was a clinical rejection and there was not, so we are very happy so far with the postoperative course.

**DR. LEE FREEDMAN:**

That is marvelous, so wonderful is transplantation is for her, she doesn't even need, as you said, all the immunosuppressive therapy at least so far.

**DR. PAOLO MACCHIARINI:**

Well, this is a major advantage and I think probably the most important advantage because if we can get these in the near future for all types of transplantation, then this would change life of transplant medicine, but I am not that much optimistic to have all these steps done in the near future, probably we need years and years and years of investigations first.

**DR. LEE FREEDMAN:**

So, we are not that close. Have you done a similar procedure in any other patients at this point?

**DR. PAOLO MACCHIARINI:**

No because my specialization is the airway, so I am focusing on that. On the other hand before doing this type of transplantation, you just first need to assure that you have made all other therapeutic resources, so transplantation is something that we made in this specific case because we did not want to take off the lungs, but there are other fields of potential indications. We are now trying to improve, even improve our technique. We needed, for instance in this specific case 3 months. We are trying to get all done in 45 minutes in the operating room, but this needs at least 6 months investigation in the lab.

**DR. LEE FREEDMAN:**

You did mention that there are various growth factors that can cause a stem cell to differentiate down different paths. To your knowledge are other types of cells being developed. What kind of future do you see for this technology?

**DR. PAOLO MACCHIARINI:**

Oh, yes. I think that the future must be realistic plan, since our plan in our lab is to use differentiate the stem cells. For instance to treat patients with pulmonary hypertension, which is a lethal disease and unfortunately we do not have that many resources, except for instance lung transplantation or drugs that are very costly and most of the time in long term do not work. We have for instance evidence that by the intratracheal injection of stem cells without differentiating them, they can prevent and even reverse the pulmonary hypertension. So that we hope that we could prove evidence that in a short time, we eventually can give this therapy to patients as well. Other types of indications in my field would be for instance extend this airway transplants to patients that had larynx problems to

eventually restore the voice box or a part of the larynx which would be per se very, very, very important because the quality of life is very restricted in these patients. But for instance in the United Kingdom, there will be a clinical trial on using cartilage for meniscus operations. Can you imagine how this would change natural course of the disease? There will be indeed I think in the very short future, stem cells injection to prevent or treat myocardial infarction. So there are several indications and probably those that I have listed are the most listed to be implemented in the clinical scenario very shortly.

**DR. LEE FREEDMAN:**

So, it sounds like in the near future this technique could be used for endothelial cells for conditions like pulmonary hypertension and perhaps myocardial infarction.

**DR. PAOLO MACCHIARINI:**

Exactly.

**DR. LEE FREEDMAN:**

And in my mind, I have science fiction movies and fantasies that one day we can perhaps produce entire organs. Is that something that this technology could conceivably lead to?

**DR. PAOLO MACCHIARINI:**

Well, it could be. But I am not that optimistic that it will be in the next 20 years because we are far away from that and especially there are other types of let's say drawbacks in the sense that you know that the usage of stem cells is a very hot topic from a social point of view, political, or religious point of view. So these are things that we need to control, but as long as these applications are done under the control of ethic commissions and within the good clinical practice, I think that we will sooner or later come to the point where we can offer patients organs without using immunosuppression.

**DR. LEE FREEDMAN:**

That is marvelous. I notice that you did work with other scientists from Italy and the UK. What was their involvement?

**DR. PAOLO MACCHIARINI:**

Well, Italy was very important because on one hand University of Padua with Prof. Konkoni was responsible of controlling what we did with the human trachea in the sense that the decellularization process was blindly controlled by them and to see whether or not all cells were taken off and the University of Milan with a polytechnical institute has given use a bioreactor which is a sort of chamber where we put in the donated trachea and this chamber commits the seeding of the own patient's cells. So this commits a contact then, simultaneous on the outer and external surface. So these 2 institutions have given us a real chance to go forward in this process.

**DR. LEE FREEDMAN:**

Very nice.

Well, I would like to thank my guest from the Hospital Clinic in Barcelona Spain, Dr. Paolo Macchiarini. We have been talking about the tissue-engineered trachea transplant that he has developed and participated in. It is really a very exciting area of development. It is not something that is on the horizon for every patient, but we are starting to be able to use patient's own stem cells to help the transplantation such that some patient's may not need to be on immunosuppressive therapy after these marvelous procedures. I am Dr. Lee Freedman and I want to thank you for listening to The Clinician's Roundtable on ReachMD, The Channel For Medical Professionals.

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