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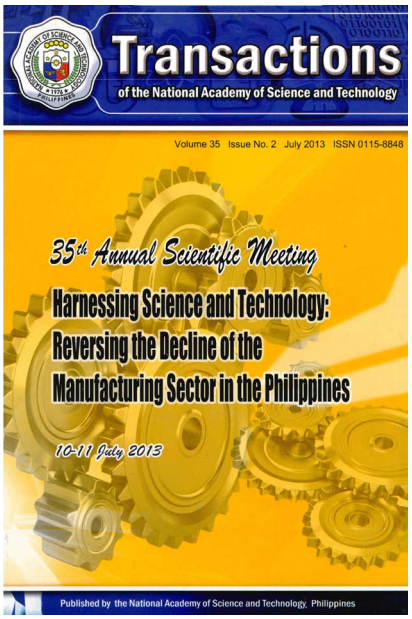

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Francisco S. Chung, Jr.

Scientific Officer, Cellular Therapeutics Lab
Associate Professor, Department of Biochemistry and Molecular Biology College of Medicine, University of the Philippines Manila

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STEM CELL THERAPY IN THE PHILIPPINES A CHANGING LANDSCAPE

Francisco S. Chung, Jr.

Scientific Officer, Cellular Therapeutics Lab
Associate Professor, Department of Biochemistry and Molecular Biology
College of Medicine, University of the Philippines Manila

Abstract

The Department of Health recently released guidelines on Stem Cell and Cell-based Therapy known as the Administrative Order 2013-0012, Rules and Regulations Governing the Accreditation of Health Facilities Engaging in Human Stem Cell and Cell-based or Cellular Therapies in the Philippines. This guideline was motivated by the massive proliferation of clinics or laboratories taking advantage of vulnerable uninitiated patients. If unabated, this unregulated procedure may harm people and impact the development of stem cell technology. Basic queries that will guide a prospective stem cell patient will be presented. To date, four hospitals are recognized by the Department of Health to practice stem-cell therapy. These hospitals are Makati Medical Center, The Medical City, National Kidney and Transplant Institute, and the Lung Center of the Philippines. This communication will focus on the current laboratory safety and monitoring practices carried out at the Cellular Therapeutics Laboratory of Makati Medical Center. The Cellular Therapeutics Laboratory is classified as ISO 14644-1 clean room ISO 5 class facility. The presentation will also feature laboratory standards such as autologous Cell Transplant release criteria and critical quality control tests. The future of Stem Cell Therapy will be profoundly influenced by the clinicians, scientists, regulatory offices, media, and society, who are in position to distinguish the difference between science and fiction. Patients who are left with limited clinical options are often entangled; wading through the investigative and controversial scientific breakthroughs is a tight walk.

Keywords: Stem cell, cell-based therapy, cell transplant

Good morning everyone. Firstly, I would like to thank the organizing committee of National Academy of Science and Technology for giving me

an opportunity to present the changing landscape of stem cell therapy in the Philippines. It is also nice to see familiar faces, former mentors, and colleagues.

I will not have a long introduction about stem cell because most likely, all of you must have heard about it and it has been in the news for quite some time now. My purpose is to enlighten some of the misconceptions about stem cell therapy. Now, this will be the outline of my presentation. I have the introduction, FAQ's on stem cells and what is happening in the Philippines in the area of stem cell transplantation and what do we see in the future.

Briefly, I will characterize or describe stem cell. Thus, they have remarkable ability to develop into any different cell types in the body during our lifetime. They can also work like a repair system. They could divide essentially without limit to replace damaged tissues or cells. For example, if you have been drinking heavily on alcohol, we have liver stem cell that will replace our liver provided that you have activated your liver stem cell. Same thing with our heart, in our lungs, etc. Now, the third description of stem cell is quite new because this is the basis of Dr. Shinya Yamanaka and Dr. John Gurdon's win of the Nobel Prize last year.

If you have specific condition, physiological condition, or genetic lithography, you could induce ordinary cell to become stem cell. Hence, this stem cell can be re-programmed to function as a specialized tissue. To give you a picture where we source the stem cell, let me emphasize that commonly, we are very much familiar with stem cell being sourced out from embryonic or tissue stem cells. Subsequently, because this is a rapidly evolving science, we could also harvest stem cell from adult. So again, let me emphasize most of the transplantation being done in our country are being sourced out in the adult individual. So we call it, adult stem cell. Now, from the adult, we can get it from the bone marrow, we can get it from specific tissues. If you are going to get it from the skin, you could re-program it using the Yamanaka factors to become an IBS and from IBS convert it to a specialized cell.

Now, in clinical application, it's been recognized as the most powerful tool or technology, the most promising technology today. So essentially, you've been hearing these almost every day in journals, every week there's publication and there are also stories of high rate of retraction. Now, if you

are going to look at the clinical trials based in the US, if you are going to visit clinicaltrials.gov, essentially, there are about 4,600 trials related to stem cell and they are in the form of IBS or induced fluid potent, embryonic, dendritic cell, umbilical cord that these are derived from bone marrow. Now what we have on the screen is a timeline in terms of development of immunotherapy. The first dendritic cell therapy derived was in 2010, so these has been approved by the USFDA and the company that developing or marketing this product is Dendreon. So, Dendreon is the first USFDA approved stem therapy based for prostate cancer. Again, just to emphasize how much it will cost for patient with refractory, hormone refractory prostate cancer to have Provisc, it will cost 90,000 US dollars. So per injection, 30,000 dollars, each patient requires 3 injections a month, so that's 90,000 dollars a month. And if you are going to look at the report, the median survival advantage is in the tune of 3.4 months. So that's very expensive, that's expensive, 90,000 dollars for a median survival of 3.4 months.

You are looking at the picture of the late, Dr. Ruth Steinman who received the Nobel Prize in Medicine in 2011. He, himself suffered from pancreatic cancer. When you talk about pancreatic cancer, we're talking about humans but he is a scientist himself, use his own dendritic cell to fight pancreatic cancer. So, he managed to prolong his life for 4 years. Unfortunately, he died before he was told of the award. So a very exceptional case for the late Dr. Steinman to received most serious award for Nobel Prize. And because of his discovery, it paved the way for therapeutic vaccines. Later on I have a caricature on how it works.

So, you have your tumor cells, you will expand this and then expose them to an environment where they would be killed. And once they are dead, they will be reducing fragments in the form of tumor antigens. This tumor antigen will be used to educate, so again, this is a form of vaccination. Once this dendritic cells, these are part of our immune system, these are excellent antigen presenting cell, once they are educated, they will transducer or co-educate other stem cells, the natural cells, the T-helper cells, these are actively involved in tumor killing or eradication.

We are not here to replace the standard of care. We know that the standard of care if you have cancer, you still have to go through chemotherapy. And what is the relationship of chemotherapy with cell based therapy like dendritic cell. So what we could see here is the ability of some

of the chemotherapeutic agents that can activate dendritic cell. They could enhance activity via cross-representation; they could enhance other T-cells. So essentially, what I am saying here is that, there is synergistic or additive effect when you combine dendritic cell and chemotherapy. If you look at the bigger picture, in yellow dots are the supposedly tumor antigen where it has been captured by the dendritic cell. It is being presented by the T-cell or the cytotoxic T-cell. So this form of education will now harm our cytotoxic T-cell to attack tumor cells. This is the colorful part done in Makati Medical Center. What we see here is a dendritic cell in green, they are labeled in green and these dendritic cells were educated to target antigen or melan antigen. Melan antigen is presented in red. This is a direct event wherein the dendritic cells are educated to target tumor antigen for melanomas.

Last year, the award for Nobel Prize was given to Yamanaka and Sir John Gurdon. It further accelerated the development of stem cell technology. Now, with this fast changing technology, there are different organizations that are involved in promoting guidelines, standardizations or limitations. These organizations are the International Society for Cellular Therapy, International Society for Stem Cell Research, and there is California Institute for Genetic Medicine. If you will visit their website, certainly, you will see guidelines or FAQ's for this type of technology and most of the slides that I will be presented later are derived from the ISFDR.

These are now the FAQ's. When you have or when you intend to get into stem cell clinic or stem cell therapy, these are the basic guidelines or questions that you would like to have before you decide to get into this controversial or investigative approach. We would like to transfer this so that most of you would be able to view it. Anyway, while waiting, I would like to address others that later on, I got the slide that I will be showing to you is the guidelines developed by the Department of Health.

There is an existing guideline developed by the Department of Health. Again, the primary objective is to protect an initiated individual in this type of therapy. If you visit the Department of Health website, you will be able to see guidelines pertaining to stem cell therapy. We have a deadline, last week of August, for clinics, laboratories, engaged in stem cell therapy. So they will start accrediting laboratories, clinics who are engaged in this type of work.

Let's continue on the FAQ's on stem cell, if you would like to consider this approach. For some of the questions that you would like to ask would be, is the treatment routine for this specific type of clinical condition. Is this part of the clinical trial and what are other options for your disease or condition? These are some of the guidelines that will help you decide whether or not taking this technology is worthwhile.

Now, if you have this type of treatment it still impacts your ability to get into a clinical trial or to have another type of treatment. And then, what are the advantages if you have this type of therapy and how it is gonna be measured objectively. So again, let me emphasize that what we see on the newspaper, you could see that this are subjective evaluation as a scientist, of course, our ideals is to measure things objectively or what are the parameters to be use to evaluate if you are responding to the treatment or not. And then another question that you would like to ask will be, is there any scientific evidence that this approach will work or possibly work your condition. And then, are they published? Were there any clinical trials pertaining to this type of treatment? Is there an internal review board or ethics review board that approved this type of therapy? And then, alternate resource persons. What are the safety guidelines in case of emergency, who will be the contact person? Who will be responsible? Were you given the rights as a patient? And the controversial question, how much?

Under Philippine setting, there are only four (4) known hospitals engaged in practicing stem cell --- Lung Center, National Kidney Transplant Institute, and two (2) private hospitals, Medical Center and Makati Medical Center.

Makati Medical Center has a clean room laboratory. When you say class 100, what does it mean? In this room, the number of particles is about 800,000 per square foot. In the stem cell laboratory, it's less than 100. How do we know? We have a particle counter. And how did we manage to do that? We have covered our ceiling by practically covering with Hepa filters. So 70-80% of the ceiling is covered by Hepa filters. If you ask me about the US standards that engage in stem cell therapy, what is the allowed particles per square foot, the answer is 10,000. So we are much cleaner. Why? Because in the area of transplantation, it is a need or it's a must to have a clean environment. But I have to emphasize that on the process being done in manipulating the cells are carried in a biosafety cabinet. Again, the particle

count in a biosafety cabinet is zero (0), it must be zero. Kung may count, there must be wrong with the cabinet. Again, we know, because we have a counter, we have a particle counter. In terms of equipments, so, we have the ability to produce clinical cellular product. I will show it to you. And then, we have experienced scientists who have about 3-4 years and a member of the International Organization for Cell Therapy (ISCP).

When you do quality control test it is at par with the international standards, transparency for disclosure and documentation of our products. This is our laboratory, you see, in order for you to work in this facility; you have to gown wearing this bunny suit. Again, why? Because the linen may contain cotton dusk that may interfere in terms of expanding the cells, you don't want contamination, you have to wear this cotton free, linen free material suit. I'm not here to promote this product, it's called Clinimax. It's capable of producing clinical-grade cell product via magnetic activated cell-sorting. In case you have your crude product, it will be combined with your antibody with iron and this is a magnet. So, iron and magnet will fish out antibody conjugated, for example to CD34. So what you will only get is positive CD34 cells, the rest will be elute in this column. So the product that we are producing is essentially of 95%. This is a magnified version. Let's say that the blue are CD34, non-CD34 are in green, yellow, no, and red.

In this, the blue CD34 positive cells were eluted remain in the column via magnet because it contains iron. If you deactivate the iron, you will end up, again, with 95% pure CD34 population. There's a recent paper published in JCO, Journal of Clinical Oncology, if you don't do CD34 selection in managing hematological malignancy, the chance of developing the graft vs host disease is 50%, that's five, zero. If you select selection, the chance of developing the graft vs host disease is 20%. Aside from producing clinical made material, we also participate in global proficiency testing. Yes, we do accept unknown specimen from US and our task is to identify colony forming groups. So far we are still waiting for the outcome of this global proficiency testing.

Just to demonstrate the quality of work that we do in this type of therapy. As I mention a while ago, there's this administrative order from the Department of Health, 2013, series number 12. So, it is gonna be evaluated hospitals, clinics will be accredited by the department of health. So deadline is August, last week of August. Aside from producing high quality cellular

products, we would like also to provide a very safe environment for the scientists. So what we are seeing right now is a panel board, it's a real time monitoring carbon dioxide-oxygen level. We need to supply carbon dioxide for the incubator in case there is leak. The air will be facilitated to be exchanged so there's a blower activated to facilitate air exchange and if there is a carbon dioxide leak in the laboratory, oxygen will also be compromised. These are audio visual alarm as a safety guideline set in the lab. And this is a typical form that we use whether we are accepting cellular product from another unit set in the hospital. These are again patterned in the international standards. We have to identify where it came from, what is the type of the sample. And we also have to check the integrity of the container. So these are the basic parameters we are looking into before we accept cellular product other stems from another facility or another unit in the hospital. Bout of the work has something to do with the QC, quality control. We test massively in terms of sterility, describing morphological characteristics of the cell, cell count, and viability. This is a typical scenario how we do cell counting and viability assay. Active in orange and propidium iodide, so, in green are the nucleated cells viable, this is non-viable cell in orange. We use thioglycolate for sterility test for the presence of microorganism. We also test for mycoplasma. We also test beta typical gel run. So, this is the subject, for example, it's negative, this is the positive control. We also test for endotoxin. This is the typical magnetic activated cell-sorting.

Now, future directions for this technology. Under Makati Med, we are at par, globally. We are following the standards, we are pursuing for the international accreditation. And we are actively involved in communications, public fora, we do acknowledge accreditation of stem cell applications and we also try for the highest quality for our cellular products. And this is the team, some of you may know some of these people --the laboratory is headed by Dr. Eric Flores and we have Monique Barile, we have a stem cell nurse, Ana Rivera, we have 2 biochemists, stem cell technologists, Alexander Lee and we have Donna, that's me and thank you for your attention.