Community HIV Cure Research Workshop - Afternoon Session – Part 1

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[00:00:36] This podcast is being presented in two parts. You are listening to part 1.

[00:00:42] Good afternoon. My name is Misha Stone and I'm a Reader Services librarian. And before we begin this admit event I would like to acknowledge that we are gathered together on the ancestral land of the Coast Salish peoples So together let us also honor their elders past and present. We thank them for their stewardship of this land as an organization committed to race and social justice. We are proud to partner with the CROI conference Fred Hutch defeatHIV and Michael Luella. Thank you. Thank you for coming to the central library. Thank you for coming to the Central Library to share information happening with HIV cure. Thank you so much for hosting this event with us. We're also honored to have Timothy Ray Brown with us again at the library and to celebrate his 12 year cure anniversary. Mandi case. Thank you so much. I'm going to turn this over to our master of ceremonies a tony Yang.

[00:01:48] Good afternoon and thank you Michael for the opportunity to moderate this afternoon session. Those of you that were with us this morning. Thank you. Those of you that were with us this morning we had a dynamic group discussion this morning and hopefully will continue this afternoon. I have the distinct and unique pleasure of introducing our first guest speaker this afternoon.

[00:02:14] And that's Dr. Karl Deven Bock. And I think I have the unique pleasure also of being able to call Karl both a I think a friend and a colleague. I've known Karl for decades and I have had the distinct honor of being able to call on him to ask him questions when I've not known something I've been able to rely on him for very direct advice when I've been lost and struggling with understanding of what to do from a unique perspective as a community member and I've always relied on him to give me an honest earnest and scientific response. So I'd like to introduce Dr. Cole defend Bock who is the director of the Division of AIDS at the National Institutes of Allergies and Infectious Disease.

[00:03:03] Nihad Khalil thank you it's a pleasure to be here. And just a word about about it Tony.

[00:03:13] She was an absolutely important person as we got started in our Washington D.C. Initiative gave us sound advice and has been a critical sounding board for us every step of the way. The first thing she said is don't make people go to the NIH to the building because we're surrounded by a fence and it just sends the wrong message. Move your clinics into town. And that was the best advice we could have had. And so I thank her for her astute stewardship and leadership in the community in Washington for the past 15 20 years.

[00:03:50] So today what I thought I would do is give a little bit of a primer on cure and talk about it from the standpoint of what does cure mean. What does it mean to cure a virus infection and use in addition HIV to other examples but then talk about something else that I think is really important for us to all to understand and that is how do we measure. What are the critical measurements we need to make in HIV what have been the game changers for assays that have come along that have made a difference in our success in fighting HIV and why I'm particularly hopeful about where we are today. Before I get into much of what you've heard already today about where the field is so Miriam Webster defines cure as a complete or permanent solution or remedy to bring about recovery from or to permanently restore health or soundness. I think that is something that we all would. We'd like to be able to achieve for HIV so what it would do what does it what happens with that. When we look at it from the perspective of the virus infections flu Hepatitis C and with HIV so on the on your right

[00:05:08] As you're looking at the screen is the graph of the flu epidemics that occur every year and as ceaseless as the tide of flu comes annually.

[00:05:22] And while we have a vaccines there are usually anywhere from 20 to 50 percent effective and the. And the lower panel shows the significant pandemics where millions of people have died. Flu is is not thought to be a big deal. However if you get it you know it's a big deal. If you're in it is incredibly infectious agent. If it's a uncomplicated flu after exposure you have a short incubation intense fever and weakness in fatigue. Up two weeks at a time and then the other concern after you've recovered is as flu evolves you got to get sick again. Because flu changes the current epidemic that we're undergoing with flu is not on this map but actually is tracking the the blue line here almost exactly. So in terms of a year it's the equivalent in the case rate is equivalent to what we saw in 16 and 17. This is where the idea you've seen a lot in the news about universal flu vaccine and there's a lot of work going on on that right now.

[00:06:39] And if we were able to get a universal flu vaccine we would drop the case rate fairly significantly so here's an example of an infection that is readily controlled by humans pretty well.

[00:06:54] However it does recur because of the variation and so the one thing that's critical to all three of these viruses is variation is a theme the natural variation in the viruses is a theme. So another virus that is also a significant public health challenge is hepatitis C or HCV. It's important to note that between 15 and 25 percent of people who become HCV positive actually clear the infection on their own within the first six months indicating that there isn't a role for immunity here that that matters. Early in infection just about everybody remains asymptomatic and progression to liver disease takes significant amount of time. And we have been able to generate a body of new

medications called direct acting antiretrovirals which creates a cure in greater than 90 percent of treat people who complete treatment that can last anywhere from as little as 8 to as much as 12 weeks. So there's a very significant advance fundamentally however if you are if you are cured via drug treatment re infection remains possible. And so there is no natural immunity that builds up with infection against Hepatitis C.. So in many ways like flu once you even know when you're cured re infection is possible and it may have to do also with that with the level of the lack of ability to generate immunity.

[00:08:31] Moving on to the virus that makes us why we're all here today. What makes HIV unique from these other two and now a central tenant in human immunology. Mouse immunology mammalian immunology is the purpose of the immune system is to activate and respond to an infection. It could be seen as a challenge to the immune system the body responds to the challenge and creates a response that pretty much most of the time clears. That challenge creates memory and rest and goes back to sleep. So think of it as a fire truck that is tailored to that specific infection. It's then it goes and puts the fire out and parks itself somewhere in the body so that at some point in the future if the body is re exposed to that same insult or agent that fire truck can come out and activate and respond. However what HIV does is it integrates it becomes part of the cell that is essential for that response. And as such as soon as that cell reactivated in response to further stimulation it further stimulates the growth of HIV. So HIV has found a way to exploit the very core tenet of immunology for its own nefarious purposes and therefore it remains a significant challenge that it is today and because it becomes part of the cellular DNA is why we actually need to talk about a cure.

[00:10:10] Because if even with antiretroviral therapy if you think about what Miriam Webster says a complete or permanent solution or a remedy or to permanently restore health antiretroviral therapy restores health but not on a permanent basis because as we are all well aware it requires at for now at least one pill once a day so why is why do I care about measurement and why should you care about measurement. And why should you be aware of what assays or technologies have come along that have made a different a difference in HIV. I think it's important for us to understand where we have been and therefore how to use those as guideposts for where we need to go in the future as we progress toward HIV a better HIV vaccine better prevention and what we need to do for an HIV cure and. Not surprisingly the first assay that came along was the blood test which allowed us to differentiate who we had become if it came infection infected with HIV and who was was not.

[00:11:26] It allowed governments around the world to protect the blood supply to diagnose those particularly early in disease. Because as we were all are well aware Frank AIDS was obvious but who who actually was going to progressed to AIDS was not known. But it wasn't until we had first the blood test and it wasn't until we had a blood test that we were able to then figure out that the CDC for test would be a good marker for disease progression. It also demonstrated the extent of an asymptomatic period and was essential for early epidemiologic and natural history studies. So very early in the epidemic this allowed us to help begin to define what HIV was and what HIV wasn't the next test that came along. Had this relatively complex fairly dense and not very easy to understand title from a person who many of you may have heard of Jeff Lipson who is a leading scientist at the National Cancer Institute. What this was was the very first description of using polymerase chain

reaction in a quantitative way to measure the amount of virus in plasma. So this was the first example of quantitative plasma viral virus measurements. We all know and speak routinely now about viral loads. But this was the first demonstration that viral load actually mattered and the title of the paper is quite important. High levels of HIV and plasma during all stages of infection and that was the message is there's no such thing as a silent infection here. It is persistent. It's ongoing. The virus grows every day every hour all the time in the human body and it needs to and it needs to be dealt with in that kind of a way. How did this advance the field.

[00:13:29] Very quickly from 1993 on the first groups led by David Ho and Marty Markowitz and then George Shaw and his team were able to demonstrate that the drugs we were working on at that time actually had an impact on plasma viral load. And David and George's group demonstrated that the test of concept that when you provide a medication to to an individual and their viral load starts to drop you can literally measure it in days two hours. And it didn't need weeks or months or years. And that gave us the the ability to think about viral load ultimately as a surrogate. And that's why in many ways that this initial finding got us to where we are today with you equals you because without the ability to say somebody is undetectable therefore they cannot transmit. We would not be where we are today. So this is why these kinds of assays truly matter now.

[00:14:32] Where are we with essays on the cure so this paper was just published from Catherine Bruner in Bob still O'Connor's lab. Well again with a important title of quantitative approach to measuring the viral reservoir of latent HIV pro viruses and I hope in five years I can come back to an event like this and I can say to you this was the paper that has made a difference in cure because I think this essay has some specific characteristics of it which will we will be able to see if it is capable of what I hope it's capable of of being able to be the equivalent of measuring viral load. But this will be the essay for the Cure and it is a very simple essay. First and foremost it takes into account that the vast majority of the DNA that is present in our bodies if when we're on therapy that is that we're carrying in our seeds for ourselves that the pro viral DNA is defective and only about one in a thousand of those is in fact completely intact. And with Bob's lab was able to define was a region here called the Sy site which is also known as the packaging site in a region embedded in the middle of the envelope are highly conserved and for a very simple way it's essentially two PCR reactions.

[00:16:00] So again PCR is going to play a major role. But the output of the essay is brilliant it essentially looks like a flow diagram. Think about it as a form. Remember for Square when we were kids there were always. The goal was always to get into the fourth square so you were ahead serve so square one which is also known as Quadrant Three is is negative DNA no no pro virus present quadrant 1 is one of the two regions is present Quadrant Four is the other segment is present quadrant true two is both segments are present indicating that any dot in this quadrant indicates an intact pro virus. Very simple very easy and as such then is a very rapid read out and a significant improvement over the essays we currently have. Importantly this has worked well in terms of measurements in it and the group as part of this paper was able to show that by measuring these the intact virus and the the presence of one of the other two markers had different patterns of behavior within individuals over time indicating that there was as you could see significant fluctuation in the other two and a degree of stability in the Imtech pro virus.

[00:17:31] This is important now if we can get some tools that have an impact on the tech pro virus with this kind of a very simple assay that can be run in a day we'll be able to see a drop not over a course of years but days two weeks so that's why I am excited about this assay and wanted to share my enthusiasm and hope that I'm right about this and you can come back and tell me years in the future if it's not that I was full of shit. So where are we today in our path toward sustained art free remission for HIV and in many ways. Yeah there's two paths we can take we could talk about eradication of the competent HIV reservoir or classic cure or we can talk about sustained viral logic remission which would allow us to create a level of immune based control that would prevent viral rebound without in the absence of any retroviral therapy and as a famous baseball player who played for the Yankees once said Yogi Berra you come to a fork in the road take it. And so we're going to go through both.

[00:18:49] So let's talk first about what eradication would look like.

[00:18:57] And what we have in the audience with us today celebrating Timothy Ray Brown and his 12 years is is it all march to him and that there is still so much we can learn from Timothy and his case and that is is that Timothy was not only treated for one disease but he was treated for two and in some ways the. As you can see on the graph here and Timothy's story we've all heard is he had to go through two rounds of chemotherapy and two rounds of immune reconstitution. HIV was taken care of by the first but his lip but his leukemia required a second. So for four for patients like Timothy that have two diseases cancer and HIV cancer is probably the worst of the two and it's leukemia as it roared back required literally a sledgehammer like approach to help him get through his lethal cancer. Apparently at this meeting there is an example of another patient that has had a stem cell based full remission. And I have not seen the data and we all look forward to seeing the results in a Croix for that.

[00:20:18] So again congratulations Timothy. It's great to have you here for your 12th anniversary there are a range of strategies that can be used with stem cell transplantation is what we've just discussed but there's significant work has been going on recently using crisper cast 9 and other strategies for gene editing. They're modified antibodies and then the latency reversing agents so to steal a page from the defeat HIV one of their cartoons from one of their papers is this is the the places where there are multiple targets for anti HIV gene therapy and I've highlighted a couple on on this slide that you can see on if they are to work with this arrow not showing up on the screen yet the arrow on the upper right is the use of vectored antibodies. Can you take antibodies or other biologics put them in some sort of a gene therapy vector put them in the body and so that the vector will then lead to the production of this protein. This molecule that would be in the body that will serve to protect the cells from the spread of HIV.

[00:21:41] Currently we're using broad neutralizing monoclonal antibodies for prevention through studies like the AMP trial that the HIV vaccine trials network in the HIV prevention trials network are performing but it's being used also by others and more therapeutic session and more antibodies are

also being used in therapy as well. The idea would be not just to give the antibodies but actually to give the antibodies in a way that the body took care of producing it as a drug inside.

[00:22:17] The other is there's at least one talk at the meeting as well this week on engineering cells so they are genetically resistant to HIV by eliminating the CO receptor as labeled here by the Delta CCR five t cells there are several groups that have been using genetic technology to go in and edit cells so that they lack the CO receptors so they cannot be infected with HIV.

[00:22:49] Okay everyone we're going to get going again so moving on into our continued discussion this afternoon I'm going to miss this woman's name up. I went to her and tried to pronounce your name four times. She really helped me. She gave me a little pat on the shoulder and said yes. That's not it but continue. And then her friend came along and laughed at me right in my face and said Oh that's so cute you try. So I would like to introduce our next speaker.

[00:23:25] And she is going to talk to us about the potential for HIV cure from the simple cell transport trance plantation.

[00:23:36] Look at that I can even say that word and I'm going to give us Monique NYE Nice house.

[00:23:49] I guess she I guess you know her.

[00:23:52] Welcome. Thank you. I'm going to sit down now. Go Dutch. OK well

[00:24:01] Thank you very much for the nice introduction. Thank you Michael and Richard for inviting me. It's a great pleasure to be here today and to discuss with you indeed the potential for HIV cured by stem cell transplantation from the ice stem perspective. And I mainly would like to show you some of the progress that we have made within this program.

[00:24:24] So what do we know. We know that people living with HIV have a higher chance for hematological malignancies such as AML or lymphomas. And we know that they require a transplantation often with donor stem cells. And we like to call that an allergenic stem cell transplantation however we also know that people living with HIV do have an overall lower survival rate after allergenic stem cell transplantation as compared to a matched control group of HIV negative individuals. So you may wonder why are we then so interested in this particular approach. Do you have any clue yes.

[00:25:06] I think the answer to all the questions today is Timothy and he's sitting there as our guest of honor in the first relativity indeed Timothy Brown also called the Berlin patient.

[00:25:20] He was cured from both acute myeloid leukemia and from HIV infection after allergenic stem cell transplantation which cells that are called Cecil 5. Those are thirty two and this is now 12 years ago. And if I'm not mistaken we are going to celebrate this at the end of the session with cake. And that's of course the reason that I join you here today. So what is so special about this seashell

five delta 32 cells. I know that has been discussed before but I would like to take you one step back so let's have a look at each official entry. So this is the scenario where we just have wild types this year five cells here you can see very schematic representation of the virus and here you can see the cell that HIV would like to infect if you look at the virus you can see that on the outside of the fires you do have these orange spikes we call them for outflow proteins and these final harmful proteins like to attach to a city for positive cell. And that's exactly the first interaction that you see in here and afterwards the final protein will change a little bit and now it can bind to CCR five and in some instances also to another receptor called C XY or for however if we now go to the mutant situation we have cells from people from donors or just from regular individuals that have a homicide case defect and that means that they have inherited genes from the father and the mother that both have this gene defect and as a result they cannot express seizure 5 on the surface of the cell.

[00:26:56] As I've indicated on this slide and this really means that this particular virus very invested nice orange spikes can no longer infect the cells because this virus is really dependent on six year five for photo entry. So what you have done by this approach is that you really have blocked the dominant route of HIV infection however we always do have to keep in mind that there is this alternative receptor. So it might be also in these cases that in some individuals there is some six year for using fibrous lingering around somewhere in your body that will be able to use this alternative route of Pharaoh entry Well let's go back to the case of Timothy Ray Brown the Berlin patient.

[00:27:39] He was diagnosed with acute myeloid leukemia as I told you. And he received two transplant patients with cells from the same donor. He was transplanted in 2007. He received twice total body irradiation and twice severe chemotherapy. So this is quite some thing happened to his body to get him if the physician the haematologist hero who today decided to stop antiretroviral treatment at the day of transplantation. And so far no final rebound has occurred in these twelve years however before allergenic stem cell transplantation there were a few fibers fairy impressions in his blood. That's by computer algorithms where predicted to be able to use the alternative called receptor. And of course that was something that very tests haematologist that worried us in the lab. But also Timothy Ray Brown. So what we've done in Utrecht and our lab we've done some analysis by using these viruses and we check them in the lab to see what they could really infect the cells of the Berlin patient. So Dimity was very friendly to give us some of his cells and we were very fortunate to see in the laboratory that those fires although they were predicted to be able to use the alternative receptor in real life in the laboratory could not. So that was really good news so far in those 12 years. There's only one other case described. Often patients who received exactly the same kind of treatment and who stopped antiretroviral treatment and that's the so-called essence patient. So let's have a look at this patient and a little bit more detail. He was diagnosed with a particular form of lymphoma. So also a kind of blood cancer. And he was transplanted as I told you if the same kind of cells so cells licking the expression of seashell are fine. He was 27 years old so very young still when he was transplanted in 2012. Yet a very successful in graft of these donor cells.

[00:29:35] And the physicians decided to interrupt treatment one week before transplantation and they decided to do so because they were really afraid of the interactions between the chemotherapy and the antiretroviral compounds. However unfortunately the virus rebounded three weeks after

transplantation. So really really fast. And again in our laboratory in Utrecht we investigated the kind of virus. And indeed this was a fires that could use the alternative called receptor. And we also investigated in great detail the final reservoir and this particular patient before stem cell transplantation if we could demonstrate that this particular variant was already lingering around just like a minority variance in the population months before three months before stem cell transplantation.

[00:30:21] So this is very unfortunate if we now go to the situation of patients who are also receiving analogy to stem cell transplantation but now we've cells from a donor that is wild side for six year five. So these cells still express this year five on their surface. I'm sure that you're familiar with the Boston patients two patients who have been transplanted several years ago and after allergenic stem cell transplantation no HIV DNA and no infectious fibers could be detected in blood and in patient be sort of second patient also not in rectal tissue the physicians and the patients decided to interrupt treatments two point six and four point three years after transplantation respectively and final rebound was observed after 12 and 32 weeks the rebounding fighters was very much like the fighters that was already detected before transplantation in the blood like was the case in the intestine patient so there's one other case of a patient transplanted with Zetia five wild type cells in whom treatment was interrupted and what was described a literature that's the so-called Minnesota case after alleging the extreme cell transplantation HIV DNA could be detected on and off by using different very sensitive methods NPM sees however no infectious virus was detected in blood. They also looked in colon and they used a very complicated method for that as in situ hybridization and also that sensitive method was negative.

[00:31:53] So based upon these results the patient and the physician decided to interrupt treatment after two point one years and it took some time but after 41 weeks a little bit over nine year nine months virus rebounds.

[00:32:07] And if you look at the nature of this virus it doesn't look like this virus came from the blood. Unfortunately they do not really have tissue samples so we could not really determine the origin of the rebounding virus so this really leaves us with a few questions. And the main question is what Rudy determinants for cure in a Berlin patient. Why is he sitting here and why is he cured from both AML and HIV and the others are not is it the fact that cemetery already inherits one of the gene defects from one of his parents. He said that he was transplanted with the other 32 donor cells.

[00:32:45] Was it the fact that he received two transplant patients including two total body radiations and two rounds of severe chemotherapy or was it the fact that here suffered from mild graft versus host to seize after transplantation. Basically we do not know and if we want to take this one step further.

[00:33:02] We need to have insight into these mechanisms so we can translate this to other less dangerous strategies so for that reason we started the ICU STEM Consortium which is an international collaboration to guide and investigate the potential for HIV cure nature for infected patients requiring such an energy need. Stem cell transplantation for a hematological disorder the first

aim really is to guide clinicians enforced in these procedures because there's always these patients are in a hurry to get transplanted. Of course we would like to provide them with the opportunity to find a donor like Timothy Ray Brown received the second aim is also to really understand the biological mechanisms that are underlying the aggressive for reduction and a potential case of HIV cure or maybe remission or the pictures of the study I have here Martinez Ricardo and honorary evincing my colleague from University Medical Center and your dress and she sitting here in the front row if you would like to have more information you can visit our Web site and if you would like and um for is now sponsoring us for the last five years so we're very grateful for that if we are in the fun of the first things that we did was that we really looked for a donor search and we looked in a corporate bank and we also looked in the adult donor bank and if you can see here we were able to identify two hundred and thirty donors from the cord blood banks in Spain the UK Finland Germany and Sweden.

[00:34:34] And we are very grateful for hero who taught the haematologist to treat its symmetry and was able to work together with the German blood bank and they've screened more than two million donors and we've been able to have not 22000 donors lacking shelf life expression. So this is really a big step forward.

[00:34:56] If we now look to our cohort we have 45 patients registered from nine different countries eight in Europe and Canada. Of those 45 patients thirty nine patients have been transplanted and 26 patients are still alive. The median follow up is over 4.5 years and 19 patients are now beyond the first year after transplantation and here you can see the breakup of all the different numbers. Most patients were treated with cells from adult donors some with cord blood most of the patients received seizure five wild type or his or psycho cells. And in total nine patients received cells lacking the expression of CCR five four of those patients are still alive and twenty two patients received wild ball type or heads or psycho cells are still alive so going back to our second aim it's really important for us to be able to measure these reductions in the final reservoir and for that we've developed very sensitive techniques. We've developed an essay that can detect only one copy of HIV RNA and turn million plus one or CHF. We have detected a method for detection of HIV DNA in millions of cells and we've developed a method to detect one single infectious virus particle again in millions of cells.

[00:36:15] If we are not looking at HIV DNA and if we are looking at HIV RNA we really have to keep in mind that if we look at those genome based detection methods that all the different viral variants that are circulating worldwide and also to come back to the question of most earlier if we want HIV cure an HIV cure research to be globally accessible will we really have to come up with these methods that cannot only detect HIV shipped IDB that is circulating in the US and in Europe. But we also have to take into account all the different subtypes worldwide. So this is something that we have done and we are have published last summer with only having very sensitive methods is not enough.

[00:36:57] We also need access to the HIV reservoir and I'm sure that you've heard a lot about the HIV reservoir today. Here you can see a scheme with the different compartments here we have peripheral blood and all the cells that we think might play a role as a reservoir cell. The lymph nodes you even have an anatomical compartment the central nervous system and we are afraid that HIV might be hiding and different issues and especially in the alien. So how do we work in our system.

What we do is we first ask a patient just for one single tube of blood and then we look whether we can still find HIV DNA what we can find infectious fires and if we can still find it there's no need to do do any other analysis. We just asked to repeat the same analysis three months later but if we cannot detect anything any HIV DNA any infectious fighters we ask for lack of resources and in that case we get access to one billion to 10 billion cells that are potentially infected with HIV. So still it's looking for a needle in a haystack but we we really are going to investigate whether we can find any evidence of HIV and if we can find no evidence of HIV we asked the patient whether he or she is willing to donate bone marrow and lymph nodes.

[00:38:09] We'd like to ask to have also cerebral spinal fluid as a representative of what's going on a central nervous system. And we ask for an alien biopsy so let's have a look at the data. You can see the analysis of the dynamics of the final resting form here on the y x you can see the numbers and they really represent the HIV DNA copy per million cells. If we look at baseline so before stem cell transplantation you can see that on average 1000 HIV DNA copies can be found in one million cells. You can see also that there's a wide spread at baseline. And if we now look after transplantation you can see that there's a dramatic reduction in the HIV reservoir in the first six months. We can still detect some HIV DNA in some of the individuals but after six months the reservoir is basically empty for HIV DNA. Of course there are exceptions and I will come back to that later so you have to realize that this is so far the only curative intervention which really results in a reduction of the final reservoir in this case even a reduction to below the detection limits. You also have to keep in mind that this is still in all patients in the presence of antiretroviral treatment.

[00:39:24] So this is different still from the case of Timothy Brown and also it's interesting to note is that there's no difference between patients receiving either wild type cells or cells expressing no five so for the rest I will just focus on patients who received CHF IV wild type cells. I will come back to the other patients in my final slide so let's have a look at six of our patients all transplanted with wild type cells. And if we now look we have a single copy assay very sensitive with HIV RNA plasma. Very sensitive for HIV DNA in the cells. You can see the in five patients is undetectable. However patient 1 is the exception that I just showed you in which we can still detect a little bit of RNA and DNA if we are going to look for infectious far as you can see again that also in patient one we can still see some infectious virus. And that's the reason also why this particular facial patient we're not going to ask for Elian or CSF or anything because we know there is still HIV presence in his body but in the other patients we did get those samples from the tissue and again they are undetectable. So this is really a very promising scenario.

[00:40:39] So this brings me to my summary slides for this part.

[00:40:44] This is I. I see them as identified over 22000 CCR five delta 32 donors that can be used for allergenic stem cell transplantation in the future. I was just a mess. Compiled the largest registry of Ella transplants in people living with HIV. We have gathered all the clinical informations and we've also obtained clinical samples. We've developed an array of very sensitive techniques that can be used to analyze the final reservoir we can use for this particular study but also for our curative interventions and what we see is that after allergenic stem cell transplantation there is a sharp decline

in HIV DNA in blood CSF and tissue below the level of detection in most of the transplant patients. So what are our future directions regarding the patients transplanted with wild type cells. I've shown you the cases of the Boston patients and the Minnesota patients. So we think it's not very wise just to stop or to interrupt antiviral treatment because I'm sure that we will see also a rebound. So what we are planning to do is that we are going to do an analytical treatment interruption but with a curative intervention but for that you have to qualify you have to be clinically stable. You have to be two years post transplantation and one year post immune suppression you need to have an undetectable fatal reservoir and blood CSF and tissue and then 2019 we're going to do the first curative intervention in five patients and they will receive broadly neutralizing antibodies for eight months on the road. And these broadly neutralizing antibodies have shown to sort of give some sort of control in the regular patients who have interrupted antiviral treatments and they're going to be discussed in a plenary session at Croix in the coming week.

[00:42:30] After these eight months we will do an additional follow up of 10 months.

[00:42:34] So this is what we are planning to do with a wildfire patients so what about the patients who have been transplanted with Zetia 5.0 32 donor cells. At the moment we have four patients who receive those cells and are still alive. Data on two of these patients are going to be presented at Croix as late breaker abstracts. So what I did asked today I see certain patient number 36 is going to be presented in an oral presentation on March 5th. Eleven forty five in room six E and the data of I said patient 19 is going to be presented at the poster the day after. I'm unfortunately not allowed to say anything about these patients at the moment because otherwise the Croix police will be done and I'm sure that they will do so because the data are embargoed but I'm sure that if you go to cry it will be an exciting session both the aura and the poster session and otherwise you can see it on the webcast the day after and I'm sure that you will see something about this also in the news in the coming week. So I would like to think because this would not have been possible without the help of many many people.

[00:43:40] These are people from our own translational phonology group in your tracks. This group is headed by Maria and by myself I really would like to thank Laura who obtains all the clinical information together with our management team and she did a lot of the essays together before during and Pauline and the lab and of course I like to acknowledge all our partners from the AI STEM Consortium especially have you Martinez because I don't know what eventing what a piece of the study Kato hooter who has been instrumental in getting all these she five thirty two tests done in the donors and I really would like to thank all our partners the research work group our management team and all the contributors from all the different countries in Europe and in Canada. Of course this would not have been possible without the continued support of far so I'm very grateful for them and of course none of this would have been possible without the contribution of all the patients that are participating in this consortium.

[00:44:39] Thank you very much.

[00:44:50] You know this is truly amazing when when we first learned about Tim being cured the rate limiting factor was we don't know there's not many of these donors. You know I mean we're never gonna be able to find em and whatever and then a few years. It's it's amazing how you've identified people and gotten them registered all over Europe. I mean it's just amazing. And it's hard to believe that you felt not only found this many people but that they're you know all very willing to participate in these trials so. So we won't get the Croix police after you we won't ask you any questions but I want to ask you a different question that the participants that underwent lymph node biopsies Did you have trouble with them have an adverse events afterwards we've seen here some patients can get that lymph node biopsies with with no no problems and others have problems afterwards I mean they go away not to you know they're not horrible but we don't want them to have any any issues from me from these so compare Europe and the United States for us.

[00:45:52] Well thank you for the comment you're being very friendly. And regarding the lymph nodes you're absolutely true. So what we do is that we only take a lymph node when we can.

[00:46:02] But it's like palpable when we can really feel it. And then we will take a lymph node but if we cannot feel the lymph nodes where it's presence I mean we're not going to take any lymph node then I think that's really important because otherwise she might indeed see a lot of adverse effects.

[00:46:20] Thank you so much for this excellent talk. My question is I'm interested in those six participants and whether you are capturing any participant experiences. I mean they are undetectable now. They could be the next Tim Brown or the next Gary Stein holds which was the Boston Patient B. And we're very lucky that both Tim and Gary were very genuine sharing the experience but it would be nice to hear the participant perspective.

[00:46:48] Yeah. Again I think that's a very good comment. What we are for instance doing in our analytical treatment interruption study is that we are going to work together also with social sciences because I mean those patients may really feel that they're going to be cured from HIV infection and I'm not really sure whether they will be. So we really have we really support them with our psychologists and also we will give them a few questionnaires in order to see what they are expecting to what their expectations are and whether we can really meet those expectations.

[00:47:23] Okay. So when I I was told that you do. You do the lymph biopsy and also the get when it was discussed amongst Steven Deeks and Tim. Tim Schachter In at the University of Minnesota in Minneapolis they decided to do a very intense cold and ask me so they didn't go all the way to the gate. I'm wondering if you think that was enough.

[00:47:57] I think he is definitely enough. I think you've been folks almost everywhere including in your brain. But in our patients I think we really want to focus on those areas that we feel might be the final reservoir. If I'd really you know accessing all the different issues. So that's why would really like to have a lymph node but only if possible. We ask for CSF but only if the patients is willing to give it to us because we are still a little bit afraid of the central nervous system because we really do not get

access and it appears to be only really in reservoir. That is not reflected very well in the in the peripheral system in the blood. So that's something we really would like to have.

[00:48:35] And then on top of that we'd like to have bone marrow but but also that's not always possible cause sometimes patients are a little bit traumatized because they have given bone marrow so often during the hematological procedure that it's still you know painful for them to give it again and then we ask for an alien biopsy because we know that in this particular part of the gut there's the most lymph which associate tissue and that's really the region where if we can find a trophy we should look for just a quick comment on the lymph node biopsies I'm Jeff shouted from here in Seattle and we're doing quite a few lymph node.

[00:49:09] Finally the last spirits for vaccine studies pretty successfully getting usually about a million cells but I also do the open lymph node biopsies for our research unit here and we've had minimal morbidity and very good success an inguinal no biopsies and even without palpable nose you don't make that a criteria and we've been quite successful with minimal morbidity yet getting lymph nodes.

[00:49:29] This may be something that we should you know maybe try in the future. Also what we'd like to do is some in situ hybridization and really you would like to have you know the full length.

[00:49:40] Thank you. So I know that right now we're still not clear on which aspects of the transplant process are most important for being able to achieve viral elimination. So I'm wondering about adding the monoclonal antibodies to something that's still not well understood how you would be able to attribute you know what contributed to the success and how would you know what role the antibodies played versus the transplant itself. Yeah

[00:50:14] I think that's a fair question. Well our our initial standpoint is that if we just stop treatments in those individuals we are quite sure in the case of a wild side transplant that HIV will come back because it has been done three times and we have seen it three times. So we feel that it's more fair to our patients that we do and if intervention in those patient because you have to keep in mind that the final reservoir is either negative or like almost negative because it's really really down to maybe a few copies and maybe in that scenario just one extra push we've brought in neutralizing antibodies might be enough and that's what we're trying to do right now. And we had intensive discussions what kind of curative intervention we should do but also we have to keep in mind that these are still fragile patients. I mean they have had you know it's a logical malignancy. You know so we don't want to mess up with the immune system too much. We don't want to give them till our 7 you know agonize some things like that because we don't want you know the Leukemia Lymphoma to come back. So we really want to focus on an HIV based curative intervention. And then I think brought in those writing antibodies are the way to go and especially with the data from my mission which is why you know showing control already in two of the 10 patients that are like regular patients I'm quite hopeful that we will see some interesting data and those data might not being HIV cure but it might be that those patients are you know not showing follow rebound for a prolonged period of time.

[00:51:50] Thank you so much. My question is throughout the patients that you guys did test how many of them were did you have any there were people of color or how many people of color did you have

[00:52:04] To really be honest. I don't know if any of them had any color because for us I mean we are like a registry we don't see the patients ourselves and they are patients from all over Europe and they can be male or female that of course I would know if I would look you know back into our patients registry but we do not select our patients based on gender or race or whatever or age. I mean it's just that if patients and their physicians are interested to participate in our registry they are more than welcome we can assist them with the whole procedure and we can also offer them the most sensitive techniques to analyze what HIV is still present.

[00:52:41] Yes or no the only thing I can say what would be what kind of complicated is to find a match donor despite the fact that we've identified over 22000 we have to keep in mind that they all from the German blood bank and it could be you know that they are mostly representative of the Caucasian population.

[00:53:03] That's one thing that we do have to keep in mind because of the the Berlin patient that was one of the concerns I think is that when you we kind of look at this. It's good to have a huge impact on being something that's transferrable to people of color.

[00:53:21] Right.

[00:53:22] Yeah. So the only thing that I can say I mean I don't think also that stem cell transplantation and the way that I describe it wide right now is something that we can do like in a large majority of individuals because as I said in the beginning the mortality rate is still like almost 50 percent for these individuals. So this is definitely not like the standard curative strategy for the future but I think if we do learn about the underlying biological mechanisms we may be able to you know to translate our knowledge to the gene therapy fields and in the gene therapy field you know everybody you know can have maybe the seashell five gene modifies. So I think this is really hopeful you know for for the future but not as this is not a technique that we can do it like like like in all of us I mean that's not going to be possible.

[00:54:13] Thank you. Thank you very much.

[00:54:22] This concludes part 1. Listen to part two for the conclusion of this podcast

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