

How Close is an AIDS Vaccine?

*A KUOW transcript with
Dr. Larry Corey and Dr. Julie McElrath*



Dr. Larry Corey



Dr. Julie McElrath

Marcy Sillman: You're listening to Weekday on 94.9 FM KUOW Seattle, KUOW 1340 AM Tumwater, Olympia, streaming online at KUOW.org. This is Tuesday, June 20th, 2006. I'm Marcy Sillman in for Steve Share.

More than 40 million people around the world are living with AIDS or HIV. Although the rate of infection has slowed down somewhat in some African and Caribbean nations, 5 million people were newly infected with HIV in 2004, 3 million people died of AIDS-related illnesses that same year.

Scientists around the world have been working together to develop a vaccine that would help prevent HIV infection. When will we see it in use? Joining us today to talk about the very challenging task of developing an AIDS vaccine are Dr. Larry Corey. He is Principal Investigator of the HIV Vaccine Trials Network, head of the University of Washington's Virology Division and the Infectious Disease Program at Fred Hutchinson Cancer Research Center. Thank you for coming in today.

Dr. Larry Corey: Happy to be here, Marcy.

Marcy Sillman: Also with us is Dr. Julie McElrath. She is Principal Investigator for the HIV Vaccine Trials Network's Seattle site. She is a Professor of Medicine at the University of Washington and a member of the Clinical Research Division at the Hutch. Thank you for coming in as well.

Dr. Julie McElrath: Thank you, Marcy.

Marcy Sillman: Before we talk more about the specifics of the vaccine I wanted to know a little bit more about the status of HIV infection worldwide. I just said it had slowed somewhat in Africa, but I have heard that it's on the up tick in Asia. Is that correct, Dr. Corey?

Dr. Larry Corey: Yes, that's very true. India actually is now passed as far as total number of cases even Sub Sahara in Africa as far as the number of cases. And the epidemic just continues to spread worldwide. Certainly in India and China, Cambodia, Vietnam, we really are seeing increasing number of cases throughout Asia. The epidemic has its characteristics. They are often in pockets of areas not necessarily throughout the entire country, at least of the countries that I've named. But the virus is, unfortunately, doing quite well.

Marcy Sillman: Dr. McElrath, in this country AIDS has been identified or had been identified with the gay male community. Worldwide who are we talking about when we look at infected people?

Dr. Julie McElrath: We're more talking about heterosexuals—men and women having sex with each other and particularly on the rise are infections in women.

Marcy Sillman: Wow. Can you...when you talk about India or Sub Sahara in Africa can you give me a percentage of how many people might be infected? Is it 50%, 60%?

Dr. Larry Corey: Well, in some countries of the world, especially in Sub Sahara in Africa the prevalence is between 20 and 30%. In fact, there are some calculations that have been done if you're a 15-year-old boy or girl and living in Botswana or the Republic of South Africa you eventually will have an 85% chance of dying of AIDS during your lifetime. So those are very sobering characteristics.

In Asia and India those figures are really much, much different. Again, there is much of a less generalized epidemic and there are certainly pockets, but the virus has shown its ability to be very adaptable and to spread into many populations unless control measures are developed.

Marcy Sillman: I believe it was the 25th anniversary of the HIV...the first recorded case in the United States...not a happy occasion to celebrate, but in that time in this country at least we've seen the development of treatment drugs, effective drugs that make this a disease that you could survive with for the most part?

Dr. Larry Corey: Well, the development of HIV therapy has been one of the great success stories of medicine. We have seen from all the patients that we used to take care of who did not survive, now they are thriving. Certainly there are failures. The drugs are very effective, but not without side effects. The virus is continuing to evolve and develop a resistance and it's requiring, you know, different kinds of art forms and skill to keep people productive and well. But it truly is a success story with respect to the use of combination antiretrovirals.

Marcy Sillman: Not to say that people obviously are still not done being infected with this, but I remember speaking with you...it might be almost a decade ago when the process of trying to develop a vaccine began. Was it about a decade ago? Am I right about that?

Dr. Larry Corey: Well, it's been unfortunately even longer than that. But I think when we talked it was about a decade ago.

Marcy Sillman: And both of you have been working on it that long?

Dr. Julie McElrath: Larry started a couple two to three years before I did and I joined him in 1990. And so it's been going for a long time.

Marcy Sillman: For 16 years.

Dr. Julie McElrath: Yeah.

Marcy Sillman: What was the initial challenge? I mean...the reason I asked you about the treatment drugs is because there seem to be a lot of them and the combination therapies are on the market and here 16 years later you are just in the midst of these clinical trials. So what is the first challenge for you?

Dr. Larry Corey: Well, you can say it's been a formidable walk with respect to developing a vaccine for HIV and why there has been such a success in drug therapy and there has been less of a success in vaccine development. The virus is a formidable foe with respect to its ability to change its outer coat and we still have not learned how to make vaccines that make antibodies...that make effective

antibodies because the viruses...where it lands and attaches it hides and masks itself over with a bunch of sugars and various other changes in its outer membrane and we have not really been able to effectively develop a protein or any kind of vaccine that will effectively make neutralizing antibodies. And for the first 10 or 12 years the whole field thought they knew how to do this. But we unfortunately learned that we didn't know how to do this and we went through a couple clinical trials that we thought were reasonable vaccines and they really didn't do anything.

Then the field shifted and Julie's work really was important in that showing that what we call cytotoxic t-cells or killer cells were really the kinds of cells that were controlling the virus in the blood in the body and the people who had long term progressors or many of the people who she has studied who have been exposed, but have never gotten the disease have these cytotoxic killer cells to the virus.

And about 7 or 8 years ago with her work and work done by a couple of other groups sort of demonstrated this. The field moved to saying, "Can we make vaccines that elicit these cytotoxic killer cells?" And here we've actually been a lot more successful. And we really have made over a 6 or 7 year period of time a lot of progress in developing vaccines that are achieving levels of cytotoxic killer cells that we see are effective in other vaccines.

Marcy Sillman: We're talking about the challenges to developing a vaccine that would prevent HIV infection. And with us you just heard Dr. Larry Corey. Also here Dr. Julie McElrath and we are...this is a complicated...for me particularly who's not a scientist to grasp. So I want to take you back a second, Dr. McElrath. There is, for example, a vaccination. You take your kid, they get a shot that will vaccinate them against chickenpox for example. What is different about that virus as opposed to HIV?

Dr. Julie McElrath: Yeah, the problem with HIV is that it infects cells that really help control infection. It infects CD4 cells. And these are very important helper cells of the immune system. And once you destroy those cells you really destroy your immune system. And so if you can prevent infection of those cells then you have a chance to catch up. And the idea with our vaccines is that if we...we may not be able to prevent all infections of all the cells, but if we can prevent infection of most of those cells then we have sort of a head start to get control of the virus.

Marcy Sillman: So is it just where the virus infects? Or is it also how this...the way this virus is as opposed to the way a chickenpox virus is?

Dr. Larry Corey: Well, it's both. The chickenpox virus doesn't change its outer coat and the two ways that we have made vaccines in the past, one is to...which is the way the chickenpox vaccine is made is to take the virus and pass it many times and we've learned during that period of time it makes what we call a stable deletion. So that virus is more attenuated and therefore, you know, what a vaccine is is to induce immunity but not cause illness. So in essence an attenuated kind of virus. And our measles vaccine, or live polio vaccine, our chickenpox vaccine, they are all made that way.

Now we can't do that with HIV. We've actually learned that even when you attenuate the virus and have multiple attenuations because of the way the virus replicates even a little bit it undergoes a lot more genetic recombination in the persons body and you actually get a live virus back. And there have been some studies that actually show that. So we can't use the live virus approach.

So then the other approach of the...of actually inactivating it like a flu vaccine, which is to grow the virus up and to inactivate it. I call it pickling, you know, but you sort of pickle it and hope it doesn't change its confirmation. And the salk polio vaccine was sort of that kind of growing up polio and pickling it.

Marcy Sillman: Pickled vaccine. Okay.

Dr. Larry Corey: It turns out that when we grow it up it's not in the confirmation that makes these antibodies, as well as the fact that the closed parts of the membrane that are not exposed they are still closed. And so those vacc...that approach has not worked either.

Marcy Sillman: We're talking about the many challenges facing the researchers who are trying to develop a vaccine to prevent HIV infection. Dr. Larry Corey, Dr. Julie McElrath are here and I'm envisioning one of those shooting galleries where the ducks go by except for in this case it's a duck and then it's a horse and then it's an elephant. It just keeps changing.

Dr. Julie McElrath: That's right.

Marcy Sillman: Wow. Well, we're going to take a break in just a minute, but is there a brief way, Dr. McElrath, for you to explain how you figured out which of those...that killer cell, that that was the one to target?

Dr. Julie McElrath: Yeah, the killer cell approach is a little easier because the killer cells just recognized really short peptides and those peptides are often ones that are conserved and so they don't change as much. And so it's easier to go after them. They do eventually change over time or they may be different in, you know, different strains in different countries. But you had a little better chance to go after those.

Marcy Sillman: So it's duck, duck then elephant then some ducks?

Dr. Julie McElrath: That's right.

Marcy Sillman: We're going to continue our conversation about helping to develop a vaccine that will prevent HIV infection on Weekday. Our guests, Dr. Julie McElrath and Dr. Larry Corey and this is Weekday on KUOW.

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Marcy Sillman: This is Weekday here on KUOW. I'm Marcy Sillman in for Steve Share and doctors Larry Corey and Julie McElrath are here and we're talking about the long process towards developing a very effective vaccine to prevent HIV infection. And both of you...well, Dr. Julie McElrath, you're in charge of the Seattle site of clinical trials. Dr. Corey is in charge of all the clinical trials. I understand there are about 30 vaccines, Dr. Corey, that have been developed around the world?

Dr. Larry Corey: Yes. I think the good news is, is there is a lot of effect in making an HIV vaccine. The bad news may be that we have a...we don't quite know how to direct our efforts at the moment. But I would say that what really has emerged is two or three vaccine candidates that are now really into advanced clinical development. We actually will call them efficacy trials and maybe Julie will talk about the one that's going on in Seattle. But despite all the variability of the virus there are still characteristics of HIV that make all HIV's an HIV virus and there are conserved regions of the virus. In other words areas that every HIV virus has. And those regions are really recognized by the human t-cell immune system and people who develop high t-cell based immunity to these vaccines or CD8, what we call killer t-cell immune levels, are able to control this. So we have developed some vaccines that are able to invoke in normal people...very high levels of the immune response to levels that we think should be

effective or might be effective in protecting against infection and these vaccine trials are actually ongoing.

Marcy Sillman: So when I say 30 some vaccines, these are globally? These are researchers around the world? How are their efforts coordinated?

Dr. Larry Corey: Well, about four or five years ago I think a lot of us who were working the field recognized that we didn't need...we needed, yes, more resources to move forward, to scale up some of the ideas that we had, but we also needed to collaborate and work together more closely. And we coined this term the HIV Vaccine Enterprise. Maybe it was because we were on the Star Trek ourselves. But it's a way of starting coordination and collaboration between vaccine centers and actually a lot of vaccine activity, including design activity is going on in Seattle and Julie is a leader in that area.

The worldwide network of scientists involved in HIV vaccines have really started getting together and trying to share reagents and ideas. And the funders who are making sure that the scientists behave also by doing that.

Marcy Sillman: Well, we'll talk a little bit more about funding in a while, but Dr. Julie McElrath, specific to Seattle, Dr. Corey mentioned a couple vaccines have shown some promise. How many are you testing here in Seattle?

Dr. Julie McElrath: Well, we're testing several but the main one that we're testing in larger scale trials are what we call recombinant adenovirus vectors. So these are viruses themselves that are able to allow several genes to be stuffed inside them basically. That's why they become recombinant. And so you can take some HIV genes and put them in the recombinant adenovirus vectors. None of this would cause live HIV or no one could actually get HIV as a result of receiving the vaccine.

Marcy Sillman: So when you say genes is it like a gene therapy for cancer? Is it the same kind of thing?

Dr. Julie McElrath: In a sense it's like getting infected with a virus that has a few pieces of HIV in it, but nothing that could ever cause you to get HIV as a result of receiving that vaccine. And so what it is, is as if you can make an immune response to HIV without even ever having HIV infection.

Marcy Sillman: So you're sort of trying to trick the body into thinking that HIV is there? It's not there, but it's going to make the anti-body to HIV?

Dr. Julie McElrath: That's right. And so...and the trick of simulating an infection is probably the best way to stimulate an immune response rather than to sort of passively give an antibody or passively give a protein. It's as if it can actually think it's getting infected then that is a way to really simulate more of a long-term immune response.

Marcy Sillman: You mentioned it's combined with other things. What else is it combined with?

Dr. Julie McElrath: Well, we basically take a very wimpy adenovirus, which is...adenovirus can cause...is one of the common causes of a cold in people, upper respiratory infections, but this is a very wimpy form of that.

Marcy Sillman: A wimpy cold. Okay.

Dr. Julie McElrath: A very wimpy cold. And we can stuff a number of HIV genes in it, you know, as many as three to four is what we do or we can give cocktails of these that have individual genes in them. And so once you give those and you can give them once or twice, people make an immune response to the HIV genes just like they do to the adenovirus.

Marcy Sillman: How did you know that people were going to do...respond that way? Who did you...I mean I assume you tested it on somebody before people. Right?

Dr. Julie McElrath: Yeah. These...this approach is not novel. It's been done with pox viruses, it's been done with other types, you know, of vectors. But what's important about the adenovirus vectors is that it seems to have a way to express the HIV genes in a very high level so that the immune response is just guaranteed to see it. So you can get really more vigorous immune responses than you can with some of the other vectors we've tested.

Marcy Sillman: Okay. Here's a really, really dumb question. I guess I assumed that if you were trying to develop a vaccine that the way you would test to see if it would actually prevent infection was to try to infect somebody. Obviously you don't want to do that with HIV.

Dr. Larry Corey: No.

Marcy Sillman: So how...you're just looking specifically to see if antibodies are produced and that's how you...

Dr. Larry Corey: That's the first step is to look at both antibodies and the t-cell responses, but we are really now in efficacy trials. So the trial that is going on that we called a step trial that is ongoing in Seattle at the Seattle HIV Vaccine Trials Unit, is a trial looking at the vaccine versus placebo in persons at risk for acquiring HIV and this is a trial that's done not only in the United States, but is being done in the Caribbean and South America and we're actually opening a complimentary trial of this vaccine in Sub Sahara in Africa later this summer.

So, yes, we do all the counseling we can to prevent people from being HIV, but in the United States we still have 40,000 new infections of HIV per year. That has not changed at all over the last decade. So our control of HIV via or methods is sort of stable control but we don't see the epidemic dying away. So these are truly measuring whether this will prevent HIV or even if you get HIV will it control it so that you would never develop AIDS? That's the purpose of this. And we actually think the levels of t-cell responses of this vaccine should be adequate to achieve that. Now whether it will or not is, you know, that's what the experiment is all about.

Marcy Sillman: So Dr. McElrath, what's the difference between a regular clinical trial and a step trial?

Dr. Julie McElrath: Yeah, well the step trial is the name of our trial that we're doing here in Seattle that's a large scale trial. We think of it as a step toward getting an HIV vaccine that could be available for everyone.

Marcy Sillman: So if you were going to look at all these 30 some vaccines that are in some stage of development, is the vaccine that you're testing in this trial sort of at the top of the list?

Dr. Julie McElrath: Yeah, it's moving toward...it is definitely at the top of the list, yeah.

Marcy Sillman: With a bullet is it heading up quickly or is this a slow kind of thing?

Dr. Larry Corey: Well, it emerged very quickly. I mean, yes, there are a lot of things in trial, but like all drugs about 70% of the things that enter Phase 1 never go past it. In other words we have a lot of vaccines that unfortunately a lot of effort has been done but when we put them into humans even though they worked in animals and they actually looked like they did things in non-human primates as far as immune responses the human doesn't respond to them and so they get eliminated. We send them back to the lab. We've done that unfortunately all too often, but that is the job that we have and...but it was clear that these recombinant adenovirus vectors that...which

are given by shots. So it's not like you even get a cold from them. They elicited the kinds of immune responses that other vaccines were not and to a level...and to a quantity that was really apparent to the entire field, not just to the two of us that they were worthy of moving forward and we're achieving levels that we thought might be effective.

Marcy Sillman: And so hence you're expanding the trials to these other places. We're talking about development of a vaccine that would prevent HIV infection with doctors Larry Corey and Julie McElrath and this is Weekday on KUOW. Dr. McElrath, who are you testing? Who is involved in the step trial?

Dr. Julie McElrath: We're looking for people who are not HIV infected. In Seattle for this particular trial we're primarily looking at men who may have some risk of acquiring HIV by virtue of their sexual activity. And so not all of our trials are particularly targeted toward this population, but for this particular one that's the population we're looking for.

Marcy Sillman: If you're interested in asking about these trials you can call Dr. McElrath or Dr. Corey here right now at 1-800-289-KUOW, 1-800-289-5869. So males who are sexually active with males is who you are looking for?

Dr. Julie McElrath: That's right.

Marcy Sillman: HIV negative?

Dr. Julie McElrath: That's right.

Marcy Sillman: And any other...

Dr. Julie McElrath: And healthy adults.

Marcy Sillman: Is there an age range?

Dr. Julie McElrath: We unfortunately have to cut it off at the age below 50.

Marcy Sillman: So adults above 21 and below 50?

Dr. Julie McElrath: That's right.

Marcy Sillman: What is involved for somebody who would decide to volunteer?

Dr. Julie McElrath: They need to come and learn about the trials. They need to be screened to make sure that they are eligible. Those aren't very

difficult things to do. Then they have to provide a written consent that they are willing to participate in the trial and then it is a series of visits. Some of them are a little more intense at the beginning, but then it sort of trails out towards the end. Typically our trials last between 18 months to 2 years.

Marcy Sillman: And so when you said they last longer are you studying their blood? What do you do?

Dr. Julie McElrath: Yeah, we take blood at regular intervals—not too much. We try not to take too much and we look in the blood for the appearance of both t-cells and antibodies that are responding to HIV.

Marcy Sillman: So I have to ask a question about t-cells. You hear that t-cells, t-cells, t-cell count is high, t-cell...and you called them killer cells. How do...how would somebody who has HIV...what are their t-cells like as opposed to somebody who is HIV negative?

Dr. Julie McElrath: Right. So everyone has t-cells and there are typically two types of t-cells that we're talking about. One type is called CD4 and the other type is called CD8. It's the CD4 cells that are infected by HIV and it's the CD8 cells that we're triggering with vaccines. Those are the ones that kill HIV infected CD4 cells.

Marcy Sillman: And so you're looking at their appearance or their counts? Or both?

Dr. Julie McElrath: We're looking at their appearance, the number of them, and then what they are recognizing about HIV.

Marcy Sillman: Wow. We're talking about developing a vaccine that will prevent HIV infection this hour. Doctors Julie McElrath and Larry Corey are in our studios and I'll have them both put on headphones because we do have some listeners who want to join our conversation. And if you have a question about these trials or the progress of the development of the HIV vaccine you can call 1-800-289-5869. Eric, is in his car. Hi.

Eric: Hello. Actually, a couple of questions I had just sort of what is the length of the trials? Do you guys have a sort of an end date in mind when you're going to be sort of evaluating the potential efficacy of your approach? And then I guess secondly was just sort of a comment. Having been living through the age of AIDS for so long really the comment that even though we do find...if we do, and hopefully we do find a vaccine for HIV that it still doesn't mean that condoms are not necessary because there are so many others

things that STD's that protects individuals from. So I think the...just a concern about, you know, does the joy of finding a HIV vaccine be sort of the pre-cursor to an explosion of other STD's?

Marcy Sillman: Wow.

Dr. Larry Corey: Well, those are great. The second comment is an easy one to answer because Eric is exactly right. This is a formidable agent in that even if we develop a vaccine I don't think any of us really feel it is going to be 99.9% effective. We know that a partially effective vaccine 50, 60, 70% would be a major achievement. But that also means that condoms are an important part of all STD preventions. Certainly the other disease...I've spent a lot of time in my career on genital herpes is a major factor in the acquisition rating...you're increasing the acquisition rate of HIV and condoms are an important part of the control of genital herpes. So I agree 100% with Eric's comments.

As far as the duration of the trial the trials are well thought out trials with a lot of committees looking at them and so the duration for any participant is approximately 18 months after the last vaccination. You get three shots so that's over six months so it's around 24 years...24 months. And then we follow people after that for long-term effects. But essentially the trial has a finite timeframe and is monitored by an independent safety monitoring board that actually looks at both the side effects and if there are any effects that are seen if there is any efficacy that they will review the ethics and the data from the trials and decide whether to stop it early or continue it.

Marcy Sillman: So that was the question about your specific participation. Overall, Dr. McElrath, how long will this step trial continue?

Dr. Julie McElrath: We are still enrolling this trial and so once it is fully enrolled then we're looking at a 24-month window. But we certainly hope to get data from that before the completion of the 24-month period of all enrollees.

Marcy Sillman: And how many enrollees in Seattle specifically?

Dr. Julie McElrath: We're targeting 100. We would love to even get more than that. We're not quite there yet and so we're still looking for volunteers actively.

Marcy Sillman: Okay. Actively looking for volunteers. David's in Seattle. Hi. David?

David: Hi. This is David. I'm actually the nurse coordinator at the Seattle Vaccine site and I wanted to thank you folks for airing this topic. Just to clarify that these visits are short, you know, half an hour to 45-minute visits. The days of vaccine, which are only three times within the year and a half are about an hour and a half. So they are very short and for people who are out there who have said, you know, "I'm waiting for the trial that is more advanced." This is the time to step forward. This step study is going to take us to that Phase 3 trial and we would hope that you would come forward and call the (206) 667-2300 number and get involved.

Marcy Sillman: Thank you so much, David. David's coordinating...the nurse coordinator for this. This is the one he says to step forward and volunteer on. We're going to take a break right now. Doctors Julie McElrath and Larry Corey are with us talking about the work, the progress toward developing a vaccine that will prevent HIV infection. This is Weekday on 94.9 FM KUOW Seattle, KUOW 1340 AM Tumwater, Olympia.

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Marcy Sillman: This hour we're talking about viral controls or at least the search for control to HIV with doctors Larry Corey and Julie McElrath and our phone number 1-800-289-5869. I'm curious Dr. Corey, who is funding this research?

Dr. Larry Corey: Almost all of the HIV vaccine research even if it's done within the infrastructure of a pharmaceutical company is actually being funded by the U.S. government at least in the United States. There is an increasing recognition that vaccines are the technology that are probably the most cost-effective health care technology that we have. But the market for those vaccines is really not valued like a pharmaceutical product. The one pill that I'm on, Lipitor, for my cholesterol makes \$8 billion a year just in the United States. Every vaccine made and sold throughout the entire world amounts to \$8 billion and so...and here's a drug that lowers my cholesterol 50%...costs...I have to take every day, I have to get blood tests every six months. It costs a significant amount of money. If I made a vaccine like that people would say, "This is not useful," let alone the price.

Marcy Sillman: Well because you would prevent the disease and then there would be no need for other things?

Dr. Larry Corey: It's again, I guess, to some extent how we value prevention versus actually treating the disease and the costs of giving something to...worldwide like this. So there's been increasing recognition that the societal values, the public institutions that we...the value to society is actually greater than the value from the commercial point of view and therefore the public sector and the research institutions have to get into the field of vaccine development. For HIV that's been really clear that again almost all the money is fronted by the National Institute of Health. Recently The Gates Foundation has started to make large contributions to HIV vaccines, The Wellcome Trust, the European community, but this is where vaccine development is being funded. That's a good thing. So the field is really working together and you see a lot of new ideas moving forward. It took almost ten years actually to sort of...at first it was sort of left to the commercial sector to actually make vaccines. And we are recognizing that even for HIV, but for all vaccines that are important now in global health, the difficult to make vaccines, that it really is going to have to be the public sector that, and the public search institutions that actually move forward and create the kind of atmosphere that will make vaccine production. And that actually is an interesting issue even from the University's point of view because the University is not necessarily geared to actually make a product.

Marcy Sillman: Well, I wondered about that because when you look at the HIV trial website and you look at all the international trials there are some of them that have drug company names—Wyeth, Merck that are attached. So are they receiving governmental...? They are. Yes, you're nodding. The governments are paying them to make these drugs?

Dr. Larry Corey: The governments are giving them grants in a competitive way to fund the scientists who are working at the company and I personally think that that is actually quite an efficient system. It's not like the company's not using their infrastructure or their buildings or the expertise of their personnel, but the reality is that the risk is high and even if you make a vaccine I think all of us recognize that it will be the global community that will buy it and distribute it and it will be done at cost and so there is some altruism in the system. So that is the system that has evolved. And I think public/private partnerships that way are actually a good thing.

Marcy Sillman: So you talked about some of the health challenges and the fact that within the past few years you've been coordinating efforts. Political challenges...are governments coordinating efforts on this?

Dr. Larry Corey: Well, the political challenges have been formidable. First of all the virus has different types. We call them clades, which is really like a word for families and so the virus in North America is what we call Clade B and in Sub Sahara in Africa was Clade C and in India it may be Clade C, but the Indian strain was somewhat different than the South African strain and we went through a period of time where every government felt that they wanted their own vaccine because it was for their people. The reality of it was that no one could afford to make their own boutique vaccine. So that held up some stuff. Now there is a recognition that there is enough crossover here and the scientific community said there is enough crossover here so that you should be able to do this. So we're getting over that and moving forward. But certainly AIDS is a very stigmatizing disease. There are, as we say, there are no stealth HIV vaccine trials. A lot of the vaccines that we put into the protocols themselves are often debated in the individual countries parliaments.

So that takes awhile to get through some of that. Now each year we make progress. There's more and more regional approaches, regional political approaches. But the presidents and health ministries of the countries that are affected this is an important issue and they need to buy onto this and if we've been successful in doing vaccine trials in a country they always have an HIV vaccine plan that they've actually vetted and debated at a ministerial level.

Marcy Sillman: Wow. Dr. Larry Corey is with us this hour as is Dr. Julie McElrath and we're talking about the work to develop an HIV vaccine on Weekday on KUOW. And Dr. McElrath, I'm listening to these political challenges and just to go back to the step trial, which is going to expand, which is taking place in different countries. Humans I would assume, what you're hoping to see, is that the same kind of response once you inject this vaccine so if I understand what Dr. Corey is saying then with these slightly different appearances of the vaccine around the world then could you tweak the vaccine to be more specific in specific parts of the world?

Dr. Julie McElrath: Yes, you can. You can tailor them to attack the strains of a certain area. Our hope though is that we can really make a global vaccine that doesn't have to be specific for a region or a country and that it would just be universal to all. One of the studies that's a follow up to the step study is actually going to be looking at that. So can we use a strain that's more like what we're seeing in North America and Europe and find out does it work in people who are going to be

infected with a different sub type, say the one that's in Sub Sahara in Africa? Once we have that information it will just be wonderful because we can now say, "Yes, we've learned this," and we can move on. This is, I think, the thing that's key with the t-cell based vaccines that we may be able to get around this subtype clade specific problem.

Marcy Sillman: How long will it be until you know the answer to that question?

Dr. Larry Corey: Well, we should get some data from the step trial in 2007. But we will be starting this global HIV vaccine, this cocktail mixture of the cold viruses that have three separate clades all mixed up into one vaccine. And that's going to start probably mid 2007. So we'll actually start that experiment before we actually know all these data. I think at the rate of 14,000 new infections a year, 5 million a year, you know, you can just do the math to say sitting around and waiting what's the cost of that?

Marcy Sillman: Generally in the development of vaccines in this whole arena how long does it take from the time when you say, "Okay, this is going to work until the time where it's being distributed globally?"

Dr. Larry Corey: Well, that's a hard one to answer because that's going to be a function of how good it is. So I think we're approaching this to say we're trying to do the smallest trial that we can do to define whether it works or not. Recognizing that this is likely not enough data to take the vaccine to licenser. That at this point in time we need to find out whether this approach will work and how well it will work. When we have that knowledge then we really can then start the debate about is this going to be good enough to solve what the health ministers and everybody else, us as scientists, want? And so that's really where we are at the moment.

Marcy Sillman: And for that you need people to volunteer.

Dr. Julie McElrath: That's exactly right.

Marcy Sillman: That's my plug. Do you want me to give that number again?

Dr. Julie McElrath: Yes.

Marcy Sillman: The number is 667-2300 in the 206 area code. We do have some listeners who want to join this conversation. The phone number if you'd like to speak about this subject with Dr. Julie McElrath or Dr. Larry Corey is 1-800-289-5869. Hi, Linda. Thanks for holding. You're on the air.

Linda: Hi. This is a fascinating conversation. I'm really glad to hear that there is progress being made. The news I had heard a couple of years ago at a epidemiology seminar was that we probably would never have an HIV vaccine. So this is really encouraging. My question is about acceptance though down the road. I wondered if you had already thought much about issues related to acceptance similar to what we've seen already with the HPV vaccine that just got FDA approval. Already the religious right is taking a stand against it because they think it will give their kids license to go out and have sex. And so...

Marcy Sillman: You're talking about societal acceptance. I see.

Linda: Yeah. So I just thought, well, maybe because HIV is...people are much more aware of the dangers of that that it might not have the same problems as the HPV vaccine, but I just wanted to hear your opinion about that.

Marcy Sillman: That's an interesting question. Dr. Corey, do you want to take that one?

Dr. Larry Corey: Well, I think we have to look at it in global terms. I think at this point in time I'd love to have that debate. I would really love to be in the place where the HPV vaccine is now where it is almost 99% effective and yes in women, but it would be nice to have both women and men. So it would be just nice to have that debate. And I recognize what you're saying and...but yet in global terms when you look at the debate in South Africa or Malawi or even in India or China or Vietnam or Cambodia. That would be very different than the debate in the United States. I mean I would hope that from our perspective we have developed a very effective vaccine that there would be a...of a fatal disease like HIV or one that you would take all these drugs that have consequences that there would be a recognition that prevention is the best strategy. I'm not sure that you will find universal acceptance of that and I think we just do the best we can.

Marcy Sillman: Linda, thanks for that question. We'll go now to David on Bainbridge Island. Hi.

David: Hi. Thanks for taking the call. And I'd like to commend the studies that are being conducted here and that are being discussed by doctors Corey and McElrath. One of the issues of HIV...or two of the issues that they haven't really addressed here within this trial and I'd like to hear them talk about is first HIV has a way of actually

becoming dormant and some individuals can actually be infected, but cells are not necessarily expressing the determinants that would be recognized by the killer t-cells. And the second issue is that actually the CD4 cells that are the cells that are infected by HIV actually can be killed simply by HIV infection from the HIV protease. And so in fact these CD4 cells are also required for the generation of the killer cells. And so if you get rid of that specific sub population of helper cells then it creates a real problem for the efficacy of the vaccine in the long term. I'd like to hear some discussion on that.

Marcy Sillman: Well, good, thanks. I'm going to actually have Dr. McElrath explain the question to me too.

Dr. Julie McElrath: Right. Those are very good questions and very thoughtful. Obviously you have some in-depth understanding of some of the critical issues that we are dealing with. It is clear that there are, sir, there are some individuals who seem to have HIV infection where there is very low levels of virus or virtually undetectable virus. We call those long term non progressors or at least what we call are the elite long term non progressors. Those are the ones that really seem to do well and even their cytotoxic t-cell levels may be quite low because there is not much HIV that is being expressed antigenically. So those are the ones that we would like to emulate in our studies. But you do have to establish a response to begin with. And you're absolutely right that the CD4 cells can be killed by infection themselves not just by the CD8 cells and that you do need the helper cells in order to generate the CD8 cells. So the way we like to think about it is that you won't despair as many CD4 cells as you can by preventing HIV infection in these cells to begin with and then secondly even if you do have some that are infected you want to hope that the ones that remain that are not HIV infected will be functional sufficiently to be able to provide help to the CD8 killer cells. And so it's a game where you're trying to really eliminate the infection, as well as preserve the cells in order for them to maintain the immune response.

Marcy Sillman: David, thanks for that question, which I almost understand the answer to. We're just about out of time, but I wanted to just ask from potential volunteers point of view. You mentioned and I'll have you reiterate, you can't get HIV from these trials. Are there risks—health risks involved, though?

Dr. Julie McElrath: There are health risks involved with any experimental agent. And really that's the reason we do the trials in a very staged way: Phase 1, Phase 2, Phase 3 because the very most important thing

about our trials is to determine whether or not they're safe. And so there is some risk to volunteers that step up in the early stage trials because we're really trying to determine if they are safe. We clearly only go into Phase 1 trials when we have, to the best of our knowledge, information that would allow us to think this will be safe. And that there is a good chance that we could move forward with it. That there is a plausibility that it would be safe.

Marcy Sillman: So the step trial is not a Phase 1 trial though is it?

Dr. Julie McElrath: No, it's not. It's a to be trial. So we have a lot of data on it so far to suggest that the vaccine we're using in the step trial is safe.

Marcy Sillman: And if you are interested in volunteering for that, again, you can call (206) 667-2300. Thanks very much Dr. Julie McElrath. She's principal investigator at the HIV Vaccine Trials Network Seattle site, Professor of Medicine at the University of Washington, a member of the Clinical Research Division at the Fred Hutchinson Cancer Research Center. Also, many thanks to Dr. Larry Corey, the principal investigator of the HIV Vaccine Trials Network. He's head of the University of Washington's Virology Division and the Infectious Disease Program at the Hutch. This week he's a featured speaker at the Pacific Health Summit here in Seattle, as well. Thank you for coming in today.

Dr. Larry Corey: Thanks a lot, Marcy.

Marcy Sillman: This is Weekday.