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Gallo on HIV vaccines

Robert Gallo has been involved with HIV/AIDS research since the beginning of the epidemic. Together with other groups, he now seeks to start the Waterford Project, a 'Manhattan Project' for HIV vaccine research and development. He is currently the director of the Institute of Human Virology (where he also heads the Division of Basic Science), University of Maryland Biotechnology Institute in Baltimore, Maryland. Roberto Fernandez-Larsson interviewed him for AIDScience on July 19, 2001.

[AIDScience] As an introduction and in general terms, could you give us a sense of the mission and research focus of the Institute of Human Virology, which you lead?

[Robert Gallo] In terms of research we do not work only with AIDS there is some cancer and multiple sclerosis research, and some research on viruses other than HIV. However, it is recognized and will be recognized primarily as and HIV/AIDS institute. The Institute has five divisions: Clinical, Animal Model, Vaccine, Epidemiology-Prevention and Basic Science. I am the head of Basic Science. There are two general scientific goals in HIV/AIDS research:

First, to develop more biological approaches to therapy, which we hope and plan to make more feasible to the Third World that was the inspiration for the formation of the Institute. Not just the Third World, but to make therapy more palatable for the entire world, including our own country. What do I mean by biological approaches to therapy? Well, therapies that include naturally existing molecules involved in HIV infection such as cytokines, chemokines, other natural blockers of HIV, therapeutic vaccines coming out of rational research that you target to certain HIV proteins, modulation of over-produced cytokines, and augmenting some other cytokines. There are all kinds of new venues for additional HIV therapies. You could say that our chemokine discoveries of 1995, published in December of that year in Science [PubMed], that block HIV infection, were a major catalyst for the discovery of CCR5 and CXCR4. These have opened up new therapies that involve chemokines blocking HIV infection.

The second general objective is, of course, to develop a preventive HIV vaccine. The philosophy of our Institute is that the current consensus in the scientific community is a mistake, specifically the development of vaccines that limit infection but allow infection and then declare victory. I think that we cannot trust that those vaccines will work well; the virus may return full-blast. We have to go for the jugular first and do our best to develop [a vaccine that imparts] sterilizing immunity. We have not given up on that we think it is doable. The major part of our vaccine program is to prevent HIV. A preventive vaccine, in my view, is the philosophy of our Institute and is a little different from the consensus of the field today. The consensus is that we can allow infection as long as we contain the virus. I worry about that because if your vaccine succeeds allowing infection but containing the virus and not allowing disease, then 10 years from now the virus could take off. In other words, to us the goal of a preventive vaccine is sterilizing immunity complete block of infection. They say it is raising the bar it is the highest bar. We think it is doable and we think we are on a pathway to achieve it.

It is something that has worked for many viral diseases in the past.

Right, that is my view.

Besides grants to individuals by the government and others, how is the Institute funded?

The predominant funding is of course by sponsored research; NIH [U.S. National Institutes of Health] grants, a bit of funding from the pharmaceutical industry, foundations, charity, and philanthropy. Maryland State funding, which started the Institute, is now coming down like any part of the University of Maryland there is some basal funding, but it is becoming a smaller percent of the total. At one time, when we came from the NIH, of course we had no money so we were totally dependent on the state. We have now something like $23 million of sponsored research funding.

Going back to HIV vaccine research, could you give us a couple of good reasons why we do not have an HIV vaccine more than a decade and a half after the discovery of the virus?

Of course, this is a loaded question (laugh). At the very beginning, there were scientific issues that had to be settled. Okay, when were those scientific issues adequately settled? You will get different answers from different people regarding this. Some will say they are not settled yet. I could say that, roughly, five to eight years ago there was enough science and a crash program was in order. So, I think we could have gone faster. I do not mean this as an attack on any one person, persons or organizations. That is just what I think, and I tried, for example, with Project Inform leader Martin Delaney to have a crash program in 1988, but it never got off the ground. People did not believe the science was right, so the money was not there, or really the interest. Maybe I did not try hard enough, I do not know. In any case, I believe that one reason [we do not have an HIV vaccine] is we did not try as early as we should have for a crash program. I tried twice, at the beginning of the field and then when I thought the science was ready, about eight years ago. There were also scientific reasons that impaired rapid progress, including the variation of the virus and the fact that the virus integrates into DNA upon infection, it being a retrovirus. This means that the immune response has to be ready and quick if you are going to have a sterilizing immunity, to take the virus down and help to destroy a minimal number of infected cells. This entails a difficulty greater than with some other viruses.

The third and maybe underestimated difficulty is the lack of a small animal model. In fact, to the surprise of some of my scientific colleagues, I often list this as the number one problem. Think about it, if we had a small animal model. We can stick virus and vaccines into mice and rats and we can measure the immune response, but we cannot measure protection these animals do not get infected, as you know. Think about the limitations [we have] when we have to go to monkeys. How many scientists have access and money for monkeys, and how many scientists know how to work with monkeys, even if they had access to them. Also, how much longer does it take with a monkey model than it would if we had a rodent model? This is a serious handicap.

Another problem has been a general lack of total cooperation between nations, activists and scientists in the first half of the history of the field. That is now infinitely better, fostered by the informed media, and has improved things a lot. Also, [non-governmental organizations] like the Gates Foundation and the credibility that has been given to the IAVI [International AIDS Vaccine Initiative] these have catalyzed things moving forward in a more serious way.

There was never enough money for vaccines it costs so much. Also, when you have advancement sometimes you do not know how to take it to the next level. Scientists and the NIH are not equipped for practical advances; they are equipped for hypothesis-driven basic questions. When you get to the more practical [advances], it was very hard for the NIH to find the mechanism to fund someone. That is why IAVI was so important, and I think they helped catalyze the NIH moving more in that direction. We

still do not have all the practical issues solved. It still takes a lot of effort to get GMP [Good Manufacturing Practice] production and the problem of how to get the monkeys IAVI does not solve that problem. Then we have the problem of selecting which candidate [vaccine] goes forward. There are so many complications at many levels, but I think it is 10 times better than it was 5 years ago.

You are joining an AIDS vaccine effort called the Waterford Project, which will link your institution to leading researchers at Harvard and the University of California, San Francisco (UCSF).

That is correct, and also with the University of Michigan in terms of the technological issues.

Is this already a reality?

It is a reality in this sense: John Evans, who heads the Waterford Project administratively, has put up his own seed money between $1 and $2 million already. It is also a reality in that we meet and have met several times and have worked out the intellectual property rights, the fears of collaborating with another group we are not used to collaborating with, and we are sharing things pretty much equally. All those things have been worked out. What has not happened yet is the generation of the funding that John Evans and his staff are trying to raise. They are going to try hard, and it is not like they have been wasting their time; they just did not have our business plan. Now the scientists have done that and they have had it in their hands for a few months, and they are off and running.

Will other people be invited to join in the future?

The purpose of having an intense effort is to not make it open to the world. Otherwise, you have what you started from. Think about that for a moment. It sounds bad to be selective, but if you are not selective, you are back to where you were without it. Now, if I have an important collaborator to solve the problem, and in fact I have more than one, they have to be brought in. That is true of other university people too. We are not going to drop our collaborators that are key to the project. If another university decides they really want to get involved and offer us some additional intellectual things that we do not have, of course they will be added. If the whole world were involved, we would be back to ground zero, but if there is a desire of a group [to join in] and if they offer something, and we sit down and decide it will catalyze getting there quicker, of course they will be incorporated into this project. The goal is to get a vaccine. This is the noblest thing I have been involved in what we have, we have to be able to share. If the Gladstone people [the Gladstone Institute of Virology and Immunology, a Waterford Project partner] made a fundamental contribution, that went terrific, you have to take the same pride as if it were your own laboratory or your own group. We really worked on that kind of thing. Now, we are really hopeful and I think the Project is a great idea.

On the scientific side of the things, people have been talking about standardizing assays and animal trials for years. Are the participants in Waterford going to come up with a way to standardize assays, animal trials and human trials so that different vaccine candidates can be evaluated in a more meaningful way?

You know, that is a great question. I do not have an answer for you, but to answer your question, that has not been on the table. But it is a very good point. What certainly has been on the table is standardization of assays you have to have immunology cores and there has to be standards.

Will the different collaborators in the Waterford Project work in their own current projects, or

will they also collaborate in a single project?

Both. There is no doubt that you cannot stop scientific inquisitiveness and people following their patterns, but this will provide funding for collaboration. The scientific body, with scientists from all the institutions, will discuss what are our priorities in sequential order. Priority one may be something that will come from this institute, which is one of the things in discussion right now. This means that if we need help in an area that is the expertise of a Doug Nixon at UCSF, it would be his primary role in this project. Any clinical trials will be concomitantly done at each institute. That is the plan.

Some people ask, why do we need a 'Manhattan Project' in AIDS vaccine research? What are the principal stumbling blocks that impede or have impeded the academic and government establishments to reach the goal of developing an HIV vaccine in an acceptable time frame?

The answer is why not. Why would anybody ask? Why not try something different? If a person saw the substantial amount of funding needed to bring people together, and tried to synergize their efforts could he do that from the government? I suppose he could, with wit. Has it been done from the government? No it has not. This Manhattan Project is a very interesting thing. Nobody likes to make this connotation to the past, but if you think about it these guys all worked together with some self-sacrifice in the desert, right? And they got it done. We are not asking anybody to go with us. We are asking modern communication technology to put us up in some virtual room. Nonetheless, we will have human contact regularly: two or three times a year with a lot of the postdocs and everybody there. If money can be generated for that, why not do it? If you are asking me if we can do better without the government, the answer is that without the government we are nowhere. That is for basic funding, so let us not criticize the government, but is the government equipped to request that three or four people work all together? It is possible, you might be able to convince three or four people to work together, managing intellectual property, pulling a board together, telling them to collaborate in this, that and the other, and work for the common good. You might be able to pull this off by the government, but I did not see it happen.

This project also will solve problems that the government is not in the funding business for, though they try. As you know, we have also signed an arrangement with IAVI too. The two projects complement each other a lot. IAVI cannot fund this program alone no question about that. We understand that and they understand that we know that. There is no overlap between what IAVI does and what we do.

The argument against something like the Waterford Project is that the science is not there yet. I do not agree. The science has been there for a while, and I think it is a matter of doing much more trial and error than has been done. I think we need many more primate studies, or urgently developing a small animal model, and really push forward.

Is the Waterford Project similar to the group led by Marc Girard, EUROVAC?

Marc Girard is also here with me right now. He is on my board of advisors. He is also going to be the director general of the Merieux Foundation that is going to play a role in EUROVAC. I think we will be much more tightly together than they are. It is a good thing they are doing, but I would never name something "USAVAC." I believe there is a negative side, not Marc personally, but in that initiative when you have a European name. We would accept other collaborators [into the Waterford Project] immediately because of their value. We would certainly not make this project American, Chinese,

Japanese, or anything else. I think this is vulgar, obscene, to be talking about a vaccine from a person, a place. When colleagues in Europe sometimes mention and say, this will be a Swiss, an Italian, or a French vaccine, I get goose pimples. There have already been monumental contributions made by many people towards a vaccine. Some are HIV-infected people. Others, being able to grow the virus, having the molecular biology all done all these things are contributions to the vaccine. 'Waterford' at least is a neighborhood farm. John Evans would throw away the name tomorrow if somebody made the right donation to it. We suggested the name, since it was John Evan's initiative.

The thing that I absolutely find superior here [in this country], is that I do not see nationalism in U.S. science. You do not think about it nationally because you think about it as a problem that you are solving, and nobody says, 'I am going to work with the United States,' as opposed to working with Germany, for God's sake! Globalization is here. Somebody forgot to tell some parts of Europe. Why call it EUROVAC? I mean, come on! Would you not be embarrassed to hear that we named our project 'AMERICAVAC.' I am going to tell this to Marc, to change the name.

What is the concept of this "virtual lab" in the Waterford Project?

It just means that, although we do not think you can take away the need to see people, staff, postdocs and students, we will have communications set up in such a way that we can actually be in each others conferences, in the future. This seems a little bit exciting, and hopefully, there will be ways in which this can be set up, where we can make communications very, very much better.

Going to the actual science of HIV vaccines: Jon Cohen said recently that there is a fascination with new technology, and I believe he is right. In the HIV vaccine field new approaches surface constantly. He also mentioned that old vaccine technology has not been fully tested in the HIV/AIDS model. Do you think there is room, even now, for a killed whole virus approach?

Oh, Jon has a point. It never went very far, but I have to say this: some negative results never get recorded. I can certainly tell you that, at the beginning, I never threw myself fully into a vaccine, and I knew that I did not know a hell of a lot about vaccines at the time. I soon found out the vaccine community did not know a hell of a lot about retroviruses, so we both had to learn the other side. I think it was easier to learn vaccinology, than for the vaccinologists to learn retrovirology. However, we did have people that came to the NIH, and people in Fredrick, Maryland, that tried killed whole virus, independently I believe. We did not get the kind of immune response that led very far. If you ask me if I would like to see it revisited, actually I would. I do not think it was done so thoroughly, but what I saw was not exciting.

There is another angle, you have to know, and I am sure Jon has thought about it, and probably already has an answer to it. Are you sure the last particle is dead? Would you take that vaccine?

Maybe if it had been around for a while.

Yes, if you saw somebody else take it!

I recall the early Salk experience; there were vaccine failures.

That is exactly the point. Therefore, needless to say, the argument was intelligent people will never accept it at the FDA [U.S. Food and Drug Administration]. The experiments that were done were not many, and in more than one lab were not impressive.

What about the attenuated virus vaccines there are not too many folks that buy that?

You are asking the wrong person, because I was the most rigorous against it, from the moment that Ron [Desrosiers] talked about it. So I cannot change history. I already took a very strong standing since the very first set of experiments. I believe it was something worth supporting scientifically, but not to get serious anymore, even though I know some prominent scientists were pushing it, like Robin Weiss and [David] Baltimore for a while, but they had not thought it through.

Last year, you demonstrated in a *Proceedings of the National Academy of Sciences* paper [Full text article] that chemically inactivated Tat toxoid could immunize rhesus monkeys and, while not protecting them from infection, it attenuated disease effects after challenge. What are you doing with this project now, and could it become a main player in the list of vaccine alternatives in the future?

I believe so, and the answers to both your questions are yes and yes. I would never accept it as a vaccine alone. I disagree with using native Tat. We find that inactivated Tat is better than the native form, and secondly, the native form reduces the immune response to gp120. You are targeting Tat because you believe it to be immunosuppressive, and indeed it is, so why would you want to use native if you can use inactivated. We have never seen complete protection with native or inactivated Tat. We believe what we reported, we believe it could be a component of a vaccine, and in our case it will be, but that is not going to be our first major component.

What will be your first major vaccine component?

What we are pushing is a vaccine concept that came out many years ago by Franco Celada in Genoa, Italy, but I think he then moved away from it. Then a coworker, Jonathan Gershoni, came to work with me from Israel. Independently, by contract, I collaborated with Tony DeVico in ABL [Advanced BioScience Laboratories]. Now Tony is with me and Gershoni is coming back on sabbatical. The approach that Franco Celada first suggested years ago, but never really got a functional practicality, is that the combination of gp120 with CD4 is done in such a way that there is a conformational change in gp120 that we know and understand. This vaccine complex will express sites on gp120 that are, 1) conserved, and 2) sites necessary for infection to proceed. We have exciting data in this complex. DeVico, working with a senior postdoctoral fellow named Tim Fouts, has now substituted sequences in CD4 that mimic CD4. gp120 still folds back on CD4 and gives a conformation of gp120 that induces broad reactive, first ever to my knowledge, neutralizing antibodies against all the present primary isolates of HIV. We have tested about 30 of multiple clades. This has not yet been publicized or published in detail. Some of it is published, but not its major aspects.

That is the first line vaccine. The question that remains is how we are going to give it. Whether we use our Salmonella approach for mucosal immunity, whether we use it as DNA, whether we use it as protein, is under study, and we will combine that with Tat. That is our first line, and we hope to argue successfully in order for the funds to become available.

As far as the biological approaches to therapy, you have been closely involved with chemokines since the discovery that their receptors serve as entry cofactors for HIV. Much research has been done in the involvement of these receptors in the pathogenesis of HIV since then.

The chemokines discovery came first. Then Ed Burger, who was in this line of research anyway, was

further catalyzed by the chemokines discovery, and he discovered CXCR4 as co-receptor. He quickly put two and two together and found CCR5. If you use some of these chemokines per se, the turnover is too fast, and secondly sometimes they signal and you have the opposite effects, promoting instead of blocking HIV. These problems can be solved. You can add things to something like RANTES and make its half-life better. You can modify these chemokines so that they do not signal. So all the problems that people can object to, and that were tested early by a British firm, can be solved. There are things that imitate the chemokines that may be better. Shering-Plough is coming out with one that targets CCR5.

Which is the main biological approach to therapy that you are interested in?

I would say the whole area: naturally occurring inhibitors of HIV. We have defined four chemokines so far, then we discovered two more, which do not work by blocking entry.

If the Waterford Project funding becomes a reality, perhaps for the next 3 years research funding will not be a consideration for you. Assuming that will happen, what else would you want to see happening in the next 3-5 years, that is not happening now?

We will still get funding from NIH, for more basic science more likely. But clinical trials cost a fortune, as you know. If the Waterford Project raises $140 million, which is what we hope, for a period of 5 years, that is about $30 million a year. Now divide that by 3.5, and now you are talking about $8 million [for the Institute]. Is $8 million enough to do the monkey experiments, getting through the FDA and the clinical trials? Of course, it is not. We would have to go to IAVI, the Gates Foundation, the NIH, everyone you can go to to get funded. We hope that it does not backfire, if people think we do not need money.

Lastly, when you look at other groups, what do you see as the top prospect for an HIV vaccine?

I work on what I work on because I think it is the top. Obviously, if we did not think so, we would go elsewhere. So, we made our choice, and by the way, both approaches are original and both are innovative. Some of the other approaches are interesting, when properly combined. I collaborated with Pasteur-Merieux for many years on ALVAC. It is not enough. The thing that has impressed me is alphavirus [vaccine vectors], delivering HIV genes I think it is [Robert] Johnston. I think it is kind of interesting; it may be exciting.

Harriet Robinson demonstrated as much as possible that a good cell-mediated immune response can hold virus titers down, at least in the primate system with MVA [modified vaccinia Ankara] and multiple antigens [PubMed]. Osterhaus, in Rotterdam, has argued that Tat as an early antigen is a better target than some of the structural proteins which are later antigens, and I think he has demonstrated this very elegantly in recent scientific experiments. This is an idea unlike ours, where we attack Tat because we believe it to be extracellularly suppressing the immune system of uninfected cells.

I think the proper use of cytokines with the proper adjuvants will be very important for anybody's vaccine. I do believe that, like us, some people will return to humoral immunity and demonstrate that it is possible to have broadly neutralizing antibodies. Some people are already targeting in that direction, or they were already in that direction but had not achieved what they wanted yet. For example, an excellent scientist that just came to the NCI [U.S. National Cancer Institute], John Mascola, has been after the antibody approach for some time.

Finally, the reason it takes so much time is that it takes time.
