Science Translational Medicine Podcast

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Host – Annalisa VanHook
Welcome to the *Science Translational Medicine* Podcast for July 7th, 2010. I'm Annalisa VanHook, and today I'm speaking with Sam Broder, a former director of the National Cancer Institute who's currently the Chief Medical Officer at Celera. Dr. Broder led the group that pioneered the use of nucleotide analogs—such as AZT—for treating HIV infection, thus ushering in the era of antiretroviral therapies that has enabled HIV-positive individuals to live longer.

In this week's issue, Sam Broder shares his personal perspective on the rapid translation of new findings from the lab into the clinic during the early days of work on HIV and AIDS, and he explores ideas for improving and expediting translational research today.

Interviewer – Annalisa VanHook
Welcome, Dr. Broder.

Interviewee – Samuel Broder
Thank you so much. I'm glad to be talking with you.

Interviewer – Annalisa VanHook
Before HIV was identified as the causative agent of AIDS, and before HTLV-1 was identified as the causative agent of a subset of T cell lymphomas, researchers didn't seem to think it was likely that retroviruses would cause disease in humans. And even once HIV and HTLV were identified as causing disease, then people seemed to think that it might be futile to try and treat these retroviruses. Why was that idea prevalent in the scientific community?

Interviewee – Samuel Broder
The existence of animal retroviruses – that is, RNA viruses that replicate by reverse transcriptase – was already well known and widely accepted. But, there was a widespread belief that activating – that means replicating retroviruses – did not exist in human beings, partially because there had been an extensive search for them that was entirely negative. Then there was a secondary belief that even if human retroviruses did exist, they were not really involved in the pathogenesis of major human diseases. While there were some exceptions – you mentioned HTLV-1 as a cause of certain subacute T cell leukemias or, in some cases, tropical spastic paraparesis – many people felt that they, at most, played a minor role in the general public health. And then, when it was discovered and formally proven, by Gallo and Montagnier, that retroviruses really were the principle causative agent for AIDS, there was a sense of futility because it was felt that retroviruses, by their very nature, were inherently untreatable. This is for two reasons: They had a capacity to integrate into DNA of the host, and they could rapidly

mutate due to the error-prone reverse transcriptase that they possessed, and both of those factors were felt to be essentially impossible barriers to the development of effective antiretroviral therapy. So, I think that was the feeling, that was the prevailing mood that we faced in 1984 when we began thinking very seriously about trying to develop antiretroviral agents, of which the first that went through our pipeline into human beings was AZT. That was done in a collaboration of what was then called the Burroughs-Wellcome Company and also academic investigators at Duke University.

Interviewer – Annalisa VanHook
The time in between when HIV was identified as the causative agent of AIDS and the identification of the nucleotide analogs as potentially useful antiviral drugs, and then finally the human trials and approval of AZT and getting AZT into the clinic took only about 2 years…

Interviewee – Samuel Broder
It probably ranks among the most rapid timelines in modern pharmaceutical history. And I think it was a number of factors that made that possible. But, it is something that we were very fortunate to achieve.

Interviewer – Annalisa VanHook
What was there about the emergence of HIV and AIDS that enabled that – that made that happen so quickly?

Interviewee – Samuel Broder
AIDS, at the time, initially was an extremely mysterious disease, and it had appalling consequences. And it was associated with an enormous deterioration of the immune response, the onset of certain kinds of neoplasms, of which Kaposi's sarcoma is one, and it had a rapidly fatal outcome. It particularly also struck individuals in the prime of life, young individuals, and that, in turn, added an extra dimension of urgency. But, I think one of the things I want to just stress is the environment, or culture, in which a research program exists, is immensely important to this kind of discussion. I was very lucky to be part of the National Cancer Institute Intramural Program, and I think the location of my group within the Intramural Program of the National Cancer Institute had very special benefits for this antiretroviral drug discovery and development. Because first, over many years, NCI had a consistent and nearly unique commitment to search for the viral causation of cancer generally, and to identify human retroviruses specifically, largely led by Gallo and his coworkers. This kind of commitment led to the discovery and characterization of HTLV-1, the first pathogenic human retrovirus, but by the same token, there was a long-standing interest in unraveling the relationship between immunodeficiency diseases and cancer. And to add to that, the NCI, at the time, placed a very high priority on novel drug development and had considerable expertise in the clinical pharmacology and toxicology. And then the leadership at NCI at the time endorsed the philosophy that really is based on what Arthur C. Clarke has said, illustrating what it takes to break paradigms. And that is, the leadership at NCI endorsed the philosophy that, in order to discover the limits of what you think is possible, you sometimes have to go a little way past them into the territory of the impossible, and the

boundaries constantly shift, in any case. But, if you're totally afraid of crossing into the line of what might be impossible, if you're very fearful that that will make you somehow look bad or that you'll look foolish or something, you can't really make major advances, in my opinion. And the NCI really strongly supported translational medicine, although that term was not in use at the time. And last but not least, I was very fortunate in having several colleagues here – Hiroaki Mitsuya and Bob Yarchoan and others – who were able to work and tackle this problem and be unafraid of dealing with what had to be done. The other thing is, we were able, in a wholeness of motion—this is a very important point—we could, in a wholeness of motion, move from the lab to the clinic. We did not have to go through intermediaries.

Interviewer – Annalisa VanHook
Could that sort of extraordinary response happen again? Can you think of a scenario where some new emerging disease might be able to galvanize and motivate the research, the clinical, the regulatory, and the public health communities to all come together and move so fast?

Interviewee – Samuel Broder
You know, the only answer I can give to that is, "I hope so."

Interviewer – Annalisa VanHook
What about existing diseases? Do you think we could generate a movement around an existing disease, such as diabetes?

Interviewee – Samuel Broder
You can name many diseases, virtually any cancer—well, you know, breast cancer or whatever—and the answer is we have made considerable incremental progress in many diseases. In fact, diabetes was one of the models that we hoped against hope we would eventually be able to deal with. We knew that you could not eradicate HIV from the body with any of the technologies that were then available – and, by the way, we still can't do it – but we believed internally that you'd get a tangible benefit from patients. And we saw evidence of it in the clinic – we saw people getting their T4 counts going up, we saw dramatic neurological improvements in certain people, and so on. And so, the key issue is how do you act on that? We believed that eventually you'd be able to create a scenario where AIDS was like diabetes – compatible with very long survival. So, it's ironic you should bring up diabetes, but we were using that as a model. It's possible to receive a diagnosis of diabetes today, and if you're in your 40s or 50s to essentially live what amounts to a normal lifespan. You'd have to take medication, maybe insulin, and you'd have to watch your diet and so on – but, you'd be you're given an option that AIDS patients didn't have in 1985. They died quite quickly – it was an appalling disease, a terrifying, frightening disease. And so, I think you're asking an important question, and one of the reasons may be that we're used to these diseases, and that we have good, but not complete, options for many of them.

Interviewer – Annalisa VanHook
In some places, for example in the United States where patients have access to drugs and there's money for drugs, in many cases HIV infection has become a manageable condition, given the right resources. Do you think that doctors today, because they can manage HIV infection, are in any danger of becoming complacent about the epidemic?

Interviewee – Samuel Broder
I don't think they're going to be complacent, but I think there's a phenomenon that one accepts the world as it exists today as being the world that always was and always will be. So, a doctor has, in the United States, approximately 30 FDA-approved products – either single agents or important combination agents – and those are all drugs that can be used effectively, and they can suppress the virus, though not eradicate it. But, without any question that suppression of viral replication can be maintained for very long periods of time, and the patient may enjoy considerable benefit. There's been a remarkable decrease in the death rate due to AIDS and also a significant drop in the associated findings of AIDS, such as a drop in Kaposi's sarcoma and so on. So, doctors who are relatively young in their practice do not know any other time when it might have been otherwise. And so, for them the notion that people used to think HIV was inherently untreatable – that it was an exercise in futility – that notion is very alien to them. Marty Delaney one time wrote – a very famous AIDS activist – discussed the notion of false hopelessness. And that was what was going on, early on in drug development – there was a belief that nothing could be done, and that sometimes can feed on itself. Now, by the other side of the coin, it is also possible to take progress for granted, to take the state of affairs that we now have for granted. True, we cannot cure AIDS; true, virtually all the drugs available have some side effects; there's also the issue of drug resistance – those are all real issues. But, the bottom line is that the death rate has fallen in the United States and in western countries and in what we call "resource-rich countries" – and it is possible to block maternal-to-child transmission during pregnancy or shortly after pregnancy or during breast feeding and so on, a series of very dramatic advances. And people assumed that that will always be the case, and I think that assumption is something that we need to watch too, because we have to be careful that we don't enter a world of triumphalism, where we think, you know, progress is here. There are many reasons for worrying about that. The number of new cases per year, even in the United States, is still quite serious. HIV/AIDS remains a catastrophic problem in sub-Saharan Africa and in certain other parts of the world, so that nothing in our discussion should eliminate the importance of prevention, education, outreach – those are the highest priorities that one can think about. But, in the case where those do not work or have failed, we need drugs. And, of course, we need a vaccine, and hopefully there eventually will be one. But, nevertheless the number of new cases of AIDS is very significant. Drug resistance has been documented. And most worrisome to me is that transspeciation – that means going from a nonhuman primate into human beings – has also been documented, and even in modern times has been documented. So, there may be new pathogenic retroviruses in waiting in nonhuman primates that could come into human beings and create a new round of HIV/AIDS. I do not think that that is something that will happen around the corner, and hopefully it'll never happen, but it could happen, and one has to be prepared and therefore not abandon research, not abandon the view that we

need more targets for therapy, we need novel interventions, we need better ways of applying the drugs we have now. We need to worry about drug resistance, we need to know how to document drug resistance, and we need to have better approaches for viral load testing and so on. In other words, we shouldn't be complacent – we should not introduce the notion that, well, AIDS is now a manageable disorder, we can go onto to something else – I think that would be a significant error. And I think we got a foretaste of that with what happened with tuberculosis. Tuberculosis was, in one era, felt to be a disease of the past.

Interviewer – Annalisa VanHook
Right. And now we have multiply drug-resistant forms.

Interviewee – Samuel Broder
Now we have multiple drug-resistant forms and so on. So, I think we need to keep an open mind, we need to acknowledge where there has been progress, no question, and there has been considerable progress. But, I think that we cannot have triumphalism come into this arena, and we can't develop a notion that, well, we've tackled AIDS, it's under control, we can now reprogram our resources and move onto something else. The other thing I just want to emphasize is that we can't view the important needs of the public health – in particular, resource poor countries – as a competition among important priorities. This shouldn't boil down to a competition between people that think AIDS is important and people who think malaria is important. They're all important.

Interviewer – Annalisa VanHook
In your Perspective, you mention the need to adopt new paradigms for funding and for expediting the process of developing treatments and getting them into patients. And specifically, you mentioned the need for collaboration between the public and the private sectors. Why is neither sector ideally suited to successfully manage these large studies on their own, and how would the collaboration of the two be able to improve translational efforts?

Interviewee – Samuel Broder
It isn't merely the large studies that we're talking about – that's part of the equation – but actually there's a larger issue. I think that certain types of drug discovery and certain types of drug development can be done in the private sector extremely well, but the private sector cannot undertake certain types of basic research or translational research when there is a significant chance of failure and when many of the assumptions are not proven. And so, it becomes very difficult to take on certain types of very far-reaching, paradigm-shifting experiments and to move them into the clinic and to move them to registration. That requires collaboration with the academic community and with the Intramural Program of the National Institutes of Health. So, a translational medicine approach, in which the probability of success or time to completion can't be precisely quantified, would be beyond the reach of many drug development programs – quite frankly, either private or publicly funded. The other thing that I want to stress is that we need to have a wholeness of motion between the lab and the clinic. I think a compartmentalization –in which people do discovery in the lab and then almost like a

relay race, turn it over to people in the clinic who are possibly in a different administrative structure or geographic location – can work, but it does not really take the best advantage of what translational medicine means, in my opinion. So, we need to restore and replenish the notion of the wholeness of motion where clinical investigators can actually do basic research and vice versa. And I think that that is becoming more and more difficult. Think there is a specialization – it's an understandable specialization – but I think it would be important to have as many opportunities to fund, support, and train individuals who can do this wholeness of motion – that is, moving from the lab to the clinic and vice versa, from the clinic back to the lab.

Interviewer – Annalisa VanHook
Sam Broder, thank you for speaking with me.

Interviewee – Samuel Broder
Thank you so much. It was my great pleasure.

Host – Annalisa VanHook
Sam Broder is Chief Medical Officer at Celera. You can read his Perspective in this week's issue of *Science Translational Medicine*.

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