

SAGE CROSSROADS

Interview with Dr. Larry Miller Pharmaceuticals and Aging

KYLE JENSEN: Welcome to SAGE Crossroads, the premier online forum on the issues of human aging. These podcasts feature lively discussion with the experts on the ethical, political, economic, scientific, and societal implications of aging related science. Thank you for listening.

I'm joined now with Dr. Larry Miller. Dr. Miller formerly led business operations for the global Drug Discovery Division at pharmaceutical company Glaxo Smith Kline.

Dr. Miller, what do you see as the key opportunities for pharmaceutical companies in terms of aging?

LARRY MILLER: Well one thing that I think is going to be critical is that in the past, pharmaceutical companies had treated diseases of aging as discrete entities, that is to develop something for diabetes, to develop something for osteoporosis...that is to treat each one as a separate silo if you will. Then we are faced with a situation that as people get older, they have multiple conditions to treat. So then you are faced with a condition where you need to co-treat and co-administer multiple medications which then leads to the problem of having multiple side effects from multiple medications. I think the future is that scientists in companies, and in academia for that matter, will have to uncover more common pathways, so that we will be able to treat a little farther up stream so that we can treat multiple conditions at once. One example of that is these sets of sirtuin pathways that Sirtris and others are working on, and Glaxo Smith Kline is now taking up. Particular pathways that may hit a number of conditions at once. You know, this will take some courage because you're impacting a number of different pathways at once, and that tends to make managers and potentially the FDA a little shy if there are issues that go with that, but I think in the future we are going to have to look at more central regulatory pathways that are being identified now for aging.

KYLE JENSEN: Is this a relatively new concept or something that has been explored for many years?

LARRY MILLER: I think this is quite a new concept because not until recently have we begun to understand a little bit more about the aging process and find some biochemical pathways that are at the root of aging processes. People are beginning to study various tissues, for example brain, learning what types of proteins and genes are up and down regulated, turned on, turned off during aging. So I think this is all going to be a new horizon because we didn't have until now an inkling of the global aging process and how that works.

KYLE JENSEN: Now what do you see as the greatest challenges for developing drugs that deal with aging? Would you say that it's more regulatory and policy wise, or is this more scientific?

LARRY MILLER: I think there is both. When I was heading aging at Glaxo Smith Kline, the issues that I faced were that I was very interested in developing medications for frailty and weakness in muscle for when people get old because when people get weak they usually stop eating and then they fall and break a hip and end up in the hospital and die potentially, but the regulatory apparatus isn't there yet. Sarcopenia isn't recognized as an official disease by the FDA, so the pathway to get drugs approved for frailty and to get more people mobile and into society is just not there, and so it's a really difficult problem, and the pathways for osteoporosis are still very cumbersome, requiring fracture analysis. So, I think the science will come along, but I think that some of the mechanisms to get things approved are not where they need to be. There isn't an approved, for example, like Jack Coralnick uses a scale at NIH to test people's function. I think there is a critical need to have the FDA to recognize some battery of functional tests because right now we don't have a way to prove the numbers of medications that I think are important.

KYLE JENSEN: Do you have any ideas of how a reform would take place to get those things through?

LARRY MILLER: Well we have a new FDA now, hopefully, but it's going to take companies and scientists going to the FDA and to Congress to say "look the patient population is aging and currently we have a bottleneck, we can't get these medicines through" and try to work out some new policy. Hopefully, the FDA will be a little more progressive about looking at endpoints. They are very, very conservative about what endpoints they will accept. You know, there is understandably some concern that people might use these drugs and abuse them for muscle building, but on the other hand, there is a critical unmet need out there in the elderly population, and for one thing, I talked to some oncologists when I was leading aging, and if we could just keep the people healthy enough long enough for a couple more chemotherapy treatments, then that could make a big difference to somebody getting cancer treatment, so there is a lot of intertwined themes here if we could get some of these medicines approved and find a regulatory pathway, it would be important.

KYLE JENSEN: Lastly, the audience of SAGE Crossroads is made up of scientists, policy makers, and curious consumers. If there is one last statement you would like to make to them about pharmaceutical companies and aging drugs, what would it be?

LARRY MILLER: Well one thing is that it is quite difficult and expensive to develop drugs for aging per se because even to do pre-clinical models in animals is very expensive. It's very expensive to get aged animals, and they don't necessarily act like aged humans. So even in the pre-clinical stage, it's a difficult area to work in. Now that said, I think people are beginning to develop a lot of new models in yeast, in *c. elegans*, and other uni-cellular organisms that are beginning to mimic some of the pathways of aging. I don't know if you are familiar with *c. elegans*, but it's basically a little, small worm, and it has very equivalent skeletal muscle in its cell walls. When these animals age they get less mobile just as a human being and there are breaks in the muscle strands

similar to what occurs in human beings, so I think that people will have to get a little more sophisticated about using these model systems and then translating them into humans later. Again, I think from an advocacy standpoint I think it's critical for folks to go to the Hill and work with their Congressman and Senators and work with regulatory bodies to find pathways to get these drugs approved. One problem is, a lot of these companies are concerned as being seen as trying to produce "fountain of youth" drugs. I made it very clear when I was leading aging at GSK that I was not attempting simply to extend lifespan. It was around a healthy life, so there is a lot of shyness around being seen as trying to develop a frivolous drug, but again what we don't want to do is to increase lifespan and have people be frail. You don't want to live 10 more frail years. You want to have a healthy life and live a good long set of years. I think this is a policy challenge and a perceptual challenge and if you will, a public relations challenge. Again the other thing is in terms of the drug companies is that everybody is hurting right now. Drug companies are contracting, and so often, you're looking at clinical trials for aging that are quite long. Potentially, I think we need to find more intelligent, creative ways to do clinical trials using biomarkers or other types of measures where we can get the trials through quickly, and again, it goes back to the FDA policy. The FDA is going to have to be willing to accept some of these things, or we will not be able to get these drugs on the market.

KYLE JENSEN: On behalf of SAGE Crossroads, I'm Kyle Jensen.