

Longevity Science

Interview with John Q. Trojanowski

KYLE JENSEN: Welcome to SAGE Crossroads, the premier online forum in 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. John Q. Trojanowski. Dr. Trojanowski is the co-director of the center for neurodegenerative disease research and Marian S. Ware Alzheimer Drug Discovery Program and the University of Pennsylvania.

Dr. Trojanowski, what is your broad definition of a biomarker, and what can they tell us?

JOHN TROJANOWSKI: Perhaps the best quick answer to your question is there is no single definition of a biomarker. Obviously, a biomarker connotes something that marks biology, and in the field that I work in, neurodegenerative diseases, this extends from every kind of assay you might conceive of that reflects biology from a smell test; people do refer to a University of Pennsylvania smell identification test, it's a scratch and sniff test, and you recognize different odors and this interrogates, if you will, your ability to respond to odors which can decline with aging and smoking and is different in men and women and is also maybe more severely affected in disease. Some people also include neuropsychological testing as psychological biomarkers. Maybe that's a minority view, but nonetheless I just want to get that on the table, and then there is imaging biomarkers. You can image brain; you can image bone; you can tell people's ages roughly from their skeletal composition and mass, so certainly doing an x-ray on someone would help to determine aging and disease state, and then there are a lot of chemical biomarkers that are useful in many things. So this extends from something like a blood sugar test, to a pregnancy test, to tests for Alzheimer's disease. Just to state the obvious a blood sugar test measures blood sugar. If it's above a certain level, I don't know the exact numbers certainly something like 400...a blood sugar reading of 400 would almost be diabetic coma, so there are almost some blood sugar levels that are diagnostic for diabetes, but you can't always tell from clinical – what the person last ate, what they ate... It's important to point out that biomarkers don't often tell the whole story without other clinical or laboratory data. Perhaps the thing that would be the gold standard for what we would like to accomplish in aging and Alzheimer's disease is the so-called pregnancy test equivalent. A woman will know she's pregnant before she feels any of the pregnancy evolving, well before morning sickness and so forth, and you know with almost 99% certainty that because of hormones in the urine and the blood that it's pregnancy because of hormones released by the fetus and placenta, and so this predicts pregnancy. It not only shows that pregnancy is on-going, but it predicts it before people know it clinically or any other way. I say that's, you know, the gold standard or the Holy Grail because we would love to have those kind of predicted biomarkers for a whole host of aging-related conditions and certainly Alzheimer's disease. I don't mean to confuse things here, but I just wanted to let you know that biomarkers can be used for a whole host of purposes to

predict a diagnosis, predict a condition like pregnancy, to confirm a condition like pregnancy, and also to mark how a condition is progressing such as the responsive blood sugar levels to insulin, so I guess I should stop there and make sure that I haven't gotten too far a field. It's not a simple thing to give an all-purpose definition of biomarkers.

KYLE JENSEN: A big part of longevity science is that scientists are looking for the elusive biomarkers of aging. Do you think the science is in place at this time to discover these biomarkers of aging?

JOHN TROJANOWSKI: I work on this and my view on my question is very much informed by what I've learned from over 10 years of studies on Alzheimer biomarkers. So here we are talking about an aging-related disease, Alzheimer's disease, and we want to distinguish Alzheimer's from normal brain aging and normal declines in cognitive impairment and so forth, so the only question we are asking is can we see a difference between normal aging people and people with Alzheimer's disease. That very seemingly simple task has been a daunting challenge. While there are imaging and smell test biomarkers, and I've just mentioned those whole categories briefly, I've been focusing on chemical biomarkers. Looking for those in plasma or urine or cerebral spinal fluid, it's been disappointing that there are few or no plasma or urine biomarkers to Alzheimer's in controlled specificity and sensitivity levels, that is greater than 90% at all or so. This has been a great challenge. We do have biomarkers in cerebral spinal fluid that are sensitive and specific for the diagnosis, separating normal aging from Alzheimer's disease at the 90-95% level, but lumbar punctures are more invasive than a urine draw or a plasma draw, so we are not satisfied yet that we have the best biomarkers. Science is moving forward. There is no doubt that science is moving forward, but I doubt that you will be able to get a single biomarker that will globally reflect longevity, where in the lifespan someone is or how all organs are aging. Maybe there will be a panel of biomarkers, but I doubt if there will be one, and so it may be the case based on our experience with the brain that the biomarkers for Alzheimer's disease don't say anything about heart-aging, muscle-aging, skeletal-aging, and they don't say anything about any other organ except the brain, so it may be necessary to drill down as deeply into the aging processes and all other organs. We know prostate specific antigen, which goes up with cancer and can go up with aging. Here is a biomarker that is prostate specific. It may be that you look at other biomarkers for skeletal-aging and heart-aging and pancreas-aging and liver-aging and none of these in and of themselves say anything about the entire aging process of the whole organism. I think from my perspective it will be necessary to look at organ specific biomarkers if we are going to have truly informative biomarkers of successful and healthy aging versus aging that is compromised by disabilities of one kind or another due to organ failure or organ decline as a function of age.

KYLE JENSEN: Do you think that the hurdles that are preventing you all from discovering these types of biomarkers are found in funding or lack of interest in the research community? What do you see as the big block here?

JOHN TROJANOWSKI: There is a great deal of interest in these technologies that have not yet been explored in substantive depth yet, and there is clearly a limitation of funding.

There are metabolomics and proteomics and lipidomics and all these “omics” have to do with studies of lipids, proteins, and metabolites that are found in bodily fluids. There are powerful technologies to look at thousands and thousands of components in urine, plasma, cerebral spinal fluid, saliva, lachamal gland, secretions, and tears and what have you. These have not been explored yet in adequate depth. I’ll just give you one example of a study that I am involved with. Alzheimer’s disease neuroimaging study or “ADNI” was founded in 2004 with the National Institute on Aging in collaboration with about a dozen pharmaceutical companies, the Alzheimer’s Association, the Foundation for the NIH, and the National Library of Medicine I believe, but the paper will give you all the background on this. This is a five year study. Five years and 60 million dollars to look at Alzheimer’s biomarkers among the ones that I have discusses in urine, plasma, blood, and as well as imaging. 60 million dollar for a five year study that we are likely to extend in a renewal that may require another 60 million dollars. So, let us say that in 10 years that we accomplish our goals, but the cost of this is another 120 million dollars. The reason that pharma has participated and they have contributed 20 of the 60 million dollars to the study is because they desperately need information on biomarkers to reduce the cost of clinical trials for Alzheimer drugs, so they have a power incentive to want to do this, but the logistics of this study are so daunting they require 12 million dollars a year for five years to move this field forward. There are 58 or 57 sites that each see a number of patients and controls, examine those patients multiple times a year, imaging is done, fluid draws are done, and we at Penn provide the chemical biomarker analysis. There is another similar study for osteoporosis with another similar partnership formula. I don’t know the dollar amount, maybe the same or less, but these are the kind of investments that are needed to develop biomarkers that reflect aging of bone and aging of brain, as well as deviation from normal aging to become a disease process. The technologies are there; the scientists are there; the interests are there. What may be required are these partnerships. The ADNI studies are there. They are unique in its kind. There is nothing else like it. Not only because of the 60 million dollar amount, but because of the broad consortium of investigators that are required for this study in order to feed the subjects. The subjects are normal individuals 60-90, Alzheimer’s patients 60-90, if I’m wrong on the age look in the paper, and people with mild cognitive impairment which is a diagnosis that can be ascertained. This denotes, as the name implies, mild cognitive development but not dementia. These people do display a greater risk for Alzheimer’s disease if they do have mild cognitive impairment or MCI at a greater rate than individuals who have normal cognition. This is about 12-15% per year, and the interest here is to see if we can find biomarkers that reflect the transition from normal aging to MCI and then MCI to Alzheimer’s disease, so this would be of diagnostic relevance, and we’d also want markers that would reflect progression of Alzheimer’s disease. This is the kind of study and the osteoporosis study, which I know of less in detail, which needed to be duplicated or extended to other organ systems so that we will have biomarkers that reflect biomarker changes that are specific with age.

KYLE JENSEN: The audience of SAGE Crossroads is made up of scientists, policy makers, and curious consumers. If there is one closing statement closing statement you would like to make to them about biomarkers and your research, what would it be?

JOHN TROJANOWSKI: That we have all the technology. My comment to policy makers and the public is that biomarkers are fundamentally important to understanding longevity and the aging process where it is successful and healthy and has maximum function versus aging that is compromised and has disability. No time in our recent history has been as propitious or auspicious to find these biomarkers that reflect aging in different organ systems so that we could recommend treatments or enhancements to increase the quality of life for a population as they age. We should make this investment. We are the wealthiest country in the world, and our commitment is not commensurate with the talent and wealth of our country and the importance of aging to our country. We need to double and triple our efforts in this area which means doubling and tripling our resources in this area. It has to be done. I'll tell you that since January 2000, a baby boomer began to turn 60 every 7 seconds. The segment of our population over 60 is going to increase as baby boomers age. We need to do everything that we can to ensure that the quality of life in this aging population enables them to function because they are going to live a long time, and everyone would agree that is better that they are functioning, gainfully employed, and doing things that are productive for society rather than being disabled by aging related diseases that result in institutionalization or extended medical care that could bankrupt Medicare. This is a matter of great urgency and importance to many societies in countries - United States, Europe, Japan, Asia - where similar longevity trends are also taking place.

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