Interview with Stuart Kim
Evolution of Aging

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 speaking now with Dr. Stuart Kim. Dr. Kim is a professor in the Department of Developmental Biology and Genetics at the Stanford University School of Medicine.

Dr. Kim, what did your research involve that you presented for the article in *Cell*?

STUART KIM: Our research was to look at aging in the nematode c. elegan. C elegans is a great model to study the system of aging because they age in just two weeks, so it's easier to do experiments to find out what is driving the aging process. In this paper, we looked at aging between animals using micro array gene chips. This gave us a global over view of all the changes that were occurring between old and young worm. In old worms, we expected to see read outs of molecular damage like oxidative damage or shock or stress which we expected to be the causes of aging in worms. We didn't see any of that happening in the old worms. The transcriptional cascade becomes more and more unbalanced as the worms grew older, and that was the cause of the gene expression differences in the old worm.

KYLE JENSEN: Can you briefly explain the theory of developmental drift?

STUART KIM: The idea of developmental drift is that a developmental pathway that's used to make healthy tissue in normal animals is not maintained in old age. In our case, there is a developmental pathway that has three regulators, L5 – L6 – L3, whose normal job is to make particular tissues in the young worm in the intestine, and these three regulators are no longer maintained in the old worm, and so one of the developmental regulators turns down and two turn up in old age, and these become unbalanced. When these become unbalanced, the transcription factors become unbalanced and they cause myriad downstream changes in gene expression that are detrimental to the worm. All of this happens in old animals, that is after the force of natural selection has gone away. Everything we're talking about are things that happen to the homeostatic processes when nature no longer cares about homeostasis. What's going on is that in young animals, development is well balanced and then nature forgets and doesn't care anymore. The developmental pathways become unbalanced.

KYLE JENSEN: Do you feel that there is enough evidence out there with your study and other studies that favor developmental drift that would possibly outweigh evidence pointing towards other theories of aging?

STUART KIM: Well I think this is one of the first and clearest examples of developmental drift. There are some studies in mice that suggest a cell cycle repressor

called p164a might be drifting or that a wind pathway might be drifting, but these are ongoing processes, research processes, so we'll see if they pan out. I don't think it's an either or kind of question. It could certainly be partly molecular damage and partly developmental drift going on for aging. Ultimately we will have to find for each different species how much is molecular rust and how much is developmental drift.

KYLE JENSEN: What else needs to be studied to prove that this theory is true?

STUART KIM: Well for the particular set of transcription factors that drift off in old age, these are called L5 and L6, we need to find out what's upstream of that and what's upstream of that and just keep on making this pathway until we find out a little bit more of the cascade of events that are occurring that take a young worm and cause it to age in just two weeks.

KYLE JENSEN: If this theory holds true, what does it mean for aging research?

STUART KIM: We know a lot about development. Because we do, we could take new inroads and starting points to figure out what's going on with old age, so we could ask, all the developmental pathways that make young tissues and old animals, are they really misbehaving as the animals get old. Another thing it means for aging itself is why there are vast differences in life span between species. Humans and chimps differ two fold in life span. Mouse and the naked mole rat, although they are both similar kinds of rodents, differ fifteen fold in life span, so it's not easy to explain this type of life span difference with molecular damage. Animals with similar kinds of physiology have extremely different life spans, but if it's developmental drift, I could more easily understand that one species lets a particular developmental pathway accelerate or degenerate with different kinetics than another species.

KYLE JENSEN: Lastly, the audience of SAGE Crossroads is made up of scientists, policy makers, and curious consumers. If there is one last statement that you could make to them about the theory of developmental drift, what would it be?

STUART KIM: I think developmental drift is a new way to think of a mechanism for aging, and it might not only apply to worms, but it might also apply to mice and humans. What's key about developmental drift is that we already know this and we could begin by testing specific pathways in human development, and if it is, it would give us a new way to try and address issues of longevity in mammals.

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