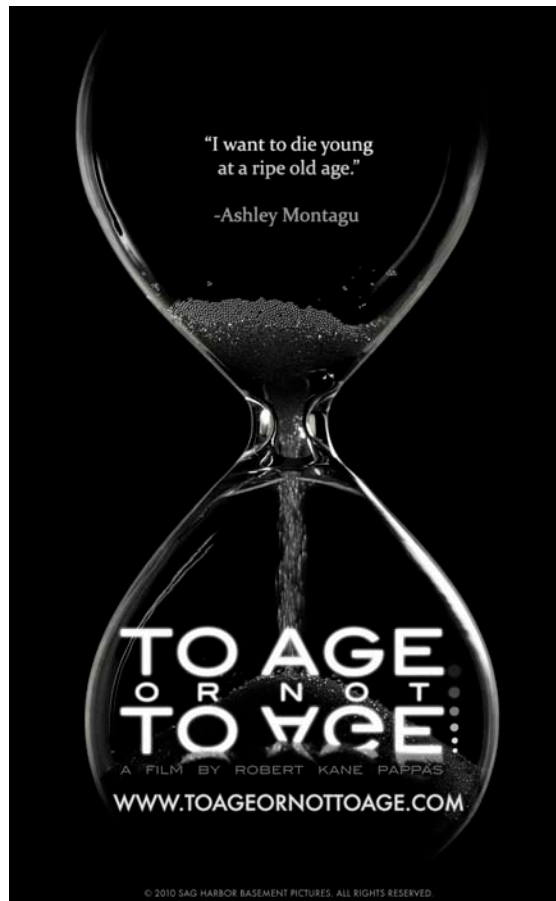


To Age Or Not To Age

A Film by Robert Kane Pappas



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Director's Statement

On Halloween (October 31st) 2006, I read the front page story in the *New York Times* Science section, regarding calorie restriction (CR) and its effects on the health and lifespan of monkeys. Two days later there was a second article beginning on the front page of the Main section, which amplified the first story.

Scientists at Harvard and MIT had been investigating the molecular biology behind calorie restriction since the early 90's, but over the past several years, one of the Harvard Scientists (Dr. David Sinclair) had identified a substance, resveratrol, found in the skin of red grapes (among other plants), that seemed to stimulate the same gene, i.e., a first generation calorie restriction mimetic. Mice fed this substance displayed some of the beneficial effects of calorie restriction.

But something else struck me about the article: the lead scientist, Dr. Sinclair, was taking resveratrol. His wife, his parents, and "half my lab" are also taking resveratrol, he said. Dr. Sinclair had studied at MIT under Dr. Leonard Guarente, who in 1995, found a gene that controlled the longevity of Yeast (Sir 2). A few years later, Dr. Sinclair teamed up with Dr. Christoph Westphal and founded the biotech company Sirtris, which, at the time of the article's publication, was doing extensive testing in both mice and humans.

So began my three-year odyssey of making *To Age or Not to Age*.

Film directors tend to be serial experts on whatever idea they happen to be seized by.

My last film investigated the structure and methodology of the mainstream news media (*Orwell Rolls In His Grave*) The film before that concerned love (*Some Fish Can Fly*). In making *To Age or Not to Age*, I probed molecular and evolutionary biology.

The questions and implications surrounding these new discoveries are nothing less than earthshaking.

To quote George Bernard Shaw:

"If you have read "*Back to Methuselah*", you will remember Franklyn Barnabas, the ex-clergyman, who with his bother, Conrad, the biologist, had come to the conclusion that the duration of human life must be extended to three hundred years, not because people would profit by a longer experience, but because it was not worth their time to make any serious attempt to better the world or their own condition when they had only thirty or forty years before they doddered away into decay and death. The Brothers Barnabas were, in fact, the first discoverers of the startlingly obvious truth that it is our expectation of life and not our experience of it that determines our conduct and character.

Consequently, the very vulgar proposition that you can not change human nature is valid only on the assumption that you can not change the duration of human life. If you can change that, you can change political conduct. It was on this thesis of the Barnabas' that I was concerned when I wrote "*Back to Methuselah*". – George Bernard Shaw

Short Synopsis

Imagine a 120-year-old living like today's 50 year-olds. Is it possible? Yes, according to the scientists in Robert Kane Pappas' new film, *To Age or Not to Age*.

Aging and death are not the absolutes we once thought they were. *To Age or Not to Age*, tracks the pioneers in the field of anti-aging research at Harvard, MIT, Cambridge and other research centers. The scientists featured in the film have found the means to postpone and possibly mitigate diseases tied to aging. That this can be done no longer seems in doubt. The only real question nowadays is “For how long?”

Long Synopsis

"This [breakthrough] ranks with the discovery of DNA... People would age more slowly, stay younger longer, and remain free of disease for a longer time." —Dr. Cynthia Kenyon

Imagine a 120-year-old living like today's 50 year-olds. Is it possible? Yes, according to the scientists in Robert Kane Pappas' new film, *To Age or Not to Age*

The scientists featured in *To Age or Not to Age* have found the means to postpone and possibly mitigate diseases tied to aging, such as cancer, cardiovascular disease and diabetes. Genes that control aging, among them SIRT2/SIRT1 genes, when altered, may increase our life span.

To Age or Not to Age, tracks the pioneers in the field of anti-aging research at Harvard, MIT, and Cambridge as well as other research centers. These scientists offer lucid commentary on this extraordinary story of discovery. Their names may soon be as well known as Watson & Crick, Einstein or Pasteur, and include Dr. Cynthia Kenyon, Dr. David Sinclair, and Dr. Leonard Guarente. (They're already being tipped as a future Nobel trifecta.) Pappas speaks to them and other leading figures in the field, including Aubrey de Grey from Cambridge – a theoretician once considered a lone gull of OxCam eccentricity – who now finds his ideas about living a 1000 years or more gaining respectability.

The paradigm shift is that aging and death are not the absolutes we once thought they were. Important breakthroughs in cell biology and our understanding of genetic hierarchies suggest that the body can be stimulated to slow down the aging process in an elegant and simple way. It all comes down to keeping our cellular repair mechanisms in working order. That this can be done no longer seems in doubt. The only real question nowadays is “For how long?” The Human condition, as we know it, is up for grabs – as

extended life (and fertility) remap all our notions about human development, success and freedom.

While *To Age or Not to Age* profiles the science of aging, it also addresses some of the moral, religious, practical and economic implications of increased, lifespan. Who will have access to the medicine? Who will benefit from the breakthroughs? Will the price of these compounds make this a drug for the elites?

There already exists a potentially catastrophic problem with overpopulation. What happens if we live even longer? What does that mean for societal structures, family, marriage, social security?

If we can postpone aging, should we? Or are we arrogantly challenging the laws of nature?

"A lot of people think we're biologically programmed to die, but the truth is that we're biologically programmed for survival. There is no mechanism inside us that turns on to kill us when a certain period of time has elapsed. —Dr. Thomas Kirkwood

Lessons Learned In “To Age Or Not To Age”

To paraphrase George Orwell... ‘the hardest thing to do on an ongoing basis is to see what’s in front of your nose.’ The greatest scientific truths are so simple that the trick is to ask the right question. An apple falls. Gravity.

The scientists in this film all agree that the major breakthroughs have involved “accidental observations” which in turn triggered questions.

With regard to the subject matter of “To Age or Not To Age,” a couple of ideas have converged recently which in combination, may well change everything. And by everything, we mean the nature of the human condition: The major breakthrough here is understanding that:

- Evolution does not care about lifespan per se, it cares about reproduction (Dr. Stephen Austad). Lifespan changes rapidly in evolutionary time and varies widely within closely related species.
- Aging and disease are molecular twins. Delay aging and you delay and mitigate virtually all disease. Extended lifespan is a side effect.
- There are a handful of regulator genes, whose activities overlap at many points in the body. These genes control the body’s repair mechanisms.
- The activity of these repair mechanisms vary from person to person, are highly heritable but also skip generations, and likely decrease with age.
- These repair mechanisms can be influenced in all the species examined so far. The question should be refashioned to: “Why NOT also in humans”
- It is precisely because evolution doesn’t care about lifespan that the scientists are making such significant strides. The scientific techniques mastered over decades coupled with computer power are accelerating these advances.

“If we tried to fix everything that is going wrong as we age it would be a hopeless task. We caught a break.” (Dr. Leonard Guarante).

Featured Interviews

Steven N. Austad, Ph.D., is a professor in the Department of Cellular & Structural Biology and the Barshop Institute for Longevity & Aging Studies at the University of Texas Health Science Center San Antonio.

Rev. Nicanor Pier Giorgio Austriaco, O.P., Ph.D., is an assistant professor of Biology and an instructor of Theology at Providence College in Providence, RI. He is also an Investigator of the Rhode Island-INBRE Program funded by the National Institutes of Health (NIH), a scientific advisor at the National Catholic Bioethics Center, and an ethicist of the Dominican Friars Health Care Ministry of New York in New York City.

Nir Barzilai, M.D., Director, Institute for Aging Research, Professor of Medicine and Molecular Genetics, Einstein College of Medicine

Troy Duster Ph.D., is Professor of Sociology at New York University and Chancellor's Professor at the University of California, Berkeley. He serves on committees for the National Academy of Sciences, the National Science Foundation, and the Legal and Social Issues Committee of the Human Genome Project

Aubrey de Grey, Ph.D., is a biomedical gerontologist; the chief science officer of SENS Foundation, a non-profit charity dedicated to combating the aging process; and editor-in-chief of *Rejuvenation Research*.

Leonard P. Guarente, Ph.D., molecular geneticist; Novartis Professor of Biology at the Massachusetts Institute of Technology; director of the Paul F. Glenn Lab for Science of Aging

Cynthia Kenyon, Ph.D., American Cancer Society Research Professor, Biochem. & Biophysics, at the University of California-San Francisco; director, UCSF Hillblom Center for the Biology of Aging

Dr. Thomas Kirkwood, professor of Medicine and Director of the Institute for Aging and Health at Newcastle University.

Gordon Lithgow, Ph.D., is a biomolecular geneticist; and head of the Lithgow Lab at the Buck Institute for Age Research.

David Sinclair, Ph.D., is director of the Paul F. Glenn Laboratories for the Biological Mechanisms of Aging at Harvard Medical School; Professor of Pathology, and a Senior Scholar of the Ellison Medical Foundation; and co-founder of Sirtris Pharmaceuticals and Genocea Biosciences.

Christoph Westphal, Ph.D., co-founder and CEO of Sirtris Pharmaceuticals.

About the Experts

Steven N. Austad, Ph.D., is a professor in the Department of Cellular & Structural Biology and the Barshop Institute for Longevity & Aging Studies at the University of Texas Health Science Center San Antonio. His current research involves the search for ways to medically slow the rate of human aging. Before moving to Texas in 2004, he held faculty positions at the University of Idaho and Harvard University. His studies involve cellular and molecular investigations of bird and mammal species that are exceptionally long- or short-lived. Dr. Austad is a multiple award-winning researcher. He is a fellow of the Gerontological Society of America, a member of the board of directors of the American Federation for Aging Research, and serves on the editorial board of most major scientific journals in the field. Dr. Austad has published more than 100 scientific papers and two books, with a third in progress. He was also co-editor (with Edward J. Masoro) of the last two editions of the *Handbook of the Biology of Aging*. His trade book, *Why We Age*, has been translated into seven languages. He formerly served on the Scientific Advisory Board of National Public Radio.

Rev. Nicanor Pier Giorgio Austriaco, O.P., Ph.D., is an Assistant Professor of Biology and an Instructor of Theology at Providence College in Providence, RI. He is also an Investigator of the Rhode Island-INBRE Program funded by the National Institutes of Health (NIH), a scientific advisor at the National Catholic Bioethics Center, and an ethicist of the Dominican Friars Health Care Ministry of New York in New York City. He earned his Ph.D. in Biology from the Massachusetts Institute of Technology, where he was a fellow of the Howard Hughes Medical Institute. At M.I.T., Fr. Austriaco worked in the laboratory of Professor Leonard Guarente on the genetics of aging in the yeast, *Saccharomyces cerevisiae*. His laboratory at Providence College is exploring the genetics of programmed cell death using the yeasts, *Saccharomyces cerevisiae* and *Candida albicans*, as model organisms. Papers describing his research have been published in *Cell*, the *Journal of Cell Biology*, and the *FEMS Yeast Research*, among others. His essays in bioethics have been published in the *National Catholic Bioethics Quarterly*, *Studia Moralia*, *Ethics and Medics*, and the *Linacre Quarterly*.

Nir Barzilai M.D. is head of the Centenarian Study at Albert Einstein College of Medicine. He studied 500 Centenarians and their children, identifying biomarkers Associated with extreme longevity.

Troy Duster Ph.D., is Professor of Sociology at New York University and Chancellor's Professor at the University of California, Berkeley. He publishes widely across the fields of the sociology of law, science, deviance, inequality, race and education. He shattered conceived notions of ethnicity in genetic research by raising the issue of race identification at the DNA level. His work proves that race continues to matter, biologically and socially. As a public intellectual, he serves on committees for the National Academy of Sciences, the National Science Foundation, and the Legal and Social Issues Committee of the Human Genome Project. In 1970, his first book, *The Legislation of Morality: Drugs, Crime, and Law* became a classic in the drug field. He is co-author of *Whitewashing Race: The Myth of a Color-Blind Society* (2003), which won

the Benjamin Hooks Award and was a finalist for the C. Wright Mills Award in 2004. Among his other awards are a Guggenheim Fellowship at the London School of Economics; an honorary Doctor of Letters from Williams College; and the Dubois-Johnson-Frazier Award from the American Sociological Association. Dr. Duster received his Ph.D. from Northwestern University.

Aubrey de Grey, Ph.D., is a biomedical gerontologist; the chief science officer of SENS Foundation, a non-profit charity dedicated to combating the aging process; and editor-in-chief of *Rejuvenation Research*. He received his BA and Ph.D. from the University of Cambridge in 1985 and 2000 respectively. His original field was computer science, and he did research in the private sector for six years in the area of software verification, before switching to biogerontology in the mid-1990s. His research interests encompass the causes of all the accumulating and eventually pathogenic molecular and cellular side-effects of metabolism (“damage”) that constitute mammalian aging, and the design of interventions to repair and/or obviate that damage. He has developed a possibly comprehensive plan for such repair, termed Strategies for Engineered Negligible Senescence (SENS), which breaks aging down into seven major classes of damage and identifies detailed approaches to addressing each one. A key aspect of SENS is that it can potentially extend healthy lifespan without limit, even though these repair processes will probably never be perfect, as the repair only needs to approach perfection rapidly enough to keep the overall level of damage below pathogenic levels. Dr. de Grey has termed this required rate of improvement of repair therapies “longevity escape velocity”. Dr. de Grey is a Fellow of both the Gerontological Society of America and the American Aging Association, and sits on the editorial and scientific advisory boards of numerous journals and organizations.

Leonard P. Guarente, Ph.D., is a molecular biologist; Novartis Professor of Biology at the Massachusetts Institute of Technology; and director of the Paul F. Glenn Lab for Science of Aging. He trained as a postdoctoral fellow at Harvard with Mark Ptashne and has been on the faculty of MIT since 1981. His lab identified SIR2 as the key gene regulating life span in yeast and *C. elegans*, and is well known for its work within the area of longevity. He is the author of over 100 scientific articles and the book *Ageless Quest: One Scientist's Search for Genes That Prolong Youth*. He is on the editorial board of *Cell*, *EMBO Reports*, *Developmental Cell*, *Genes & Development*, *Aging*, *Trends in Genetics*, and *Experimental Gerontology*, and is a member of the French Academie des Sciences, American Academy of Arts and Sciences, Academy of the American Society for Healthy Aging Investigator and American Academy of Microbiology.

Cynthia Kenyon, Ph.D., is a geneticist, the American Cancer Society Research Professor, Biochemistry and Biophysics, at the University of California-San Francisco; and director of the UCSF Hillblom Center for the Biology of Aging. She graduated valedictorian in chemistry and biochemistry from the University of Georgia in 1976, and received her PhD from MIT in 1981, where, in Graham Walker's laboratory, she was the first to look for genes on the basis of their expression profiles, discovering that DNA damaging agents activate a battery of DNA repair genes in *E. coli*. She then did postdoctoral studies with Nobel laureate Sydney Brenner at the MRC Laboratory of

Molecular Biology in Cambridge, UK, studying the development of *C. elegans*. Since 1986 she has been at the University of California, San Francisco. In 1993, Kenyon and colleagues' discovery that a single-gene mutation could double the lifespan of *C. elegans* sparked an intensive study of the molecular biology of aging. These findings have now led to the discovery that an evolutionarily conserved hormone signaling system controls aging in other organisms as well, including mammals. Dr. Kenyon has received many honors and awards for her findings. She is a member of the US National Academy of Sciences, the American Academy of Arts and Sciences, and the Institute of Medicine and she is a past president of the Genetics Society of America.

Dr. Thomas Kirkwood is Professor of Medicine and Director of the Institute for Aging and Health at Newcastle University. His research is on the basic science of aging and how genes as well as non-genetic factors, such as nutrition, influence health in old age. He led the UK Foresight Task Force on 'Healthcare and Older People' in 1995, and the 2008 Foresight project on 'Mental Capital Through Life', was Specialist Adviser to the 2005 House of Lords Science & Technology Select Committee inquiry into 'Aging: Scientific Aspects' and has served on the Councils of the UK Biotechnology and Biological Sciences Research Council and Academy of Medical Sciences. His books include the award-winning '*Time of Our Lives: The Science of Human Aging*', '*Chance, Development and Aging*' (with Caleb Finch) and '*The End of Age*' based on his BBC Reith Lectures in 2001. He was appointed a Commander of the Order of the British Empire (CBE) in 2009.

Gordon Lithgow, Ph.D., is a biomolecular geneticist; and head of the Lithgow Lab at the Buck Institute for Age Research. Dr. Lithgow coined the term Geroscience, which is a new scientific discipline focused at the intersection of normal aging and chronic disease. The program, covered in *Nature*, is funded with a prestigious National Institutes of Health "Roadmap" grant. Lithgow's lab focuses on the relationship between stress and aging by studying genes that effect lifespan and an animal's ability to resist stress. One of the most striking discoveries to come out of the Lithgow lab involves a study appearing in *Science*, which revealed that proteins that prevent cancer in humans also determine lifespan in the nematode worm *C. elegans*. In 1996, Lithgow and colleague Dr Tom Kirkwood wrote a paper for *Science*, on the "Mechanisms and Evolution of Aging", that helped make a paradigm shift away from conventional assumptions about aging. In 2000, Lithgow and Buck colleague Simon Melov, reported the first successful use of drugs to extend lifespan in an animal. The ground-breaking study, published in *Science*, involved the use of antioxidants and the nematode worm, *C. elegans*.

David Sinclair, Ph.D., is director of the Paul F. Glenn Laboratories for the Biological Mechanisms of Aging at Harvard Medical School; Professor of Pathology, and a Senior Scholar of the Ellison Medical Foundation. He has a Bachelors of Science and a Ph.D. in Molecular Genetics from the University of New South Wales, Sydney. He worked as a postdoctoral researcher at M.I.T. with Leonard Guarente, Ph.D., where he discovered a cause of aging for yeast and genes that control the aging process. He was recruited to Harvard Medical School in 1999 and was promoted to professor in 2008. In 2004, he co-

founded Sirtris Pharmaceuticals to treat age-associated diseases such as diabetes, neurodegenerative diseases, and cancer. In 2006, he co-founded Genocea Biosciences, a vaccine discovery and development company, to prevent and treat infectious diseases in developed and developing countries. Dr. Sinclair has received awards including The Australian Commonwealth Prize, a Helen Hay Whitney Postdoctoral Award, a Leukemia Society Fellowship, a Ludwig Scholarship, a Harvard-Armenise Fellowship, an American Association for Aging Research Fellowship, and a Fellowship and Senior Scholarship from the Ellison Medical Foundation. He won the Genzyme Outstanding Achievement in Biomedical Science Award (2005) and a "Bio-Innovator award" (2006).

Christoph Westphal, Ph.D., co-founded Sirtris Pharmaceuticals, Inc. in 2004 and has since served as Chief Executive Officer. In addition to leading Sirtris as an independent discovery performance unit within GlaxoSmithKline (GSK), Dr. Westphal serves as the Senior Vice President of GSK's Centre of Excellence for External Drug Discovery (CEEDD). At the CEEDD, Dr. Westphal and his team are developing a network of external alliances with world-class biotech companies to bring breakthrough medicines into the GSK pipeline. Dr. Westphal is based at Sirtris, which is located in Cambridge, Massachusetts. Dr. Westphal also serves as the Scientific Advisory Board Chair for the Healthy Lifespan Institute, and serves on the Board of Directors for Alnara Pharmaceuticals, Inc., the Board of Fellows of Harvard Medical School and the Board of Overseers of the Boston Symphony Orchestra. Dr. Westphal has been the lead or senior author on several patent applications and scientific papers in journals, including Cell, Nature and Nature Genetics.

About the Director

Robert Kane Pappas was born in New York City and raised in Westchester County. He was educated at Georgetown University and New York University Graduate Institute of Film. After graduating he worked in cable television. In the early 80's he created a non-fiction series called the "Computer Moment"; the pilot featured William H. Macy. He wrote and directed the Narrative features "Now I Know" (Lifetime Television) and "Some Fish Can Fly" (Artistic License - 99). Both films were partly set in Ireland. In 2003 he directed the Documentary Feature "Orwell Rolls In His Grave," a film that investigated the corporate conglomeration of the New Media and it's effects on our politics. The film was a culmination of a media critique that had begun when Mr. Pappas was a graduate film student at NYU during the hostage crisis and had interviewed the editor of the New York Post. Mr. Pappas has written a number of screenplays, the most recent is "Nantucket Sleighride," and had received a Parents Choice Award for his children's videos.

In his new feature documentary "To Age or not To Age" he explores the molecular biology behind aging and the degree to which we can now intervene in that process.

Credits

Writer/Director • **Robert Kane Pappas**

Producers • **Miriam Foley • Joseph Zock**

Special thanks – **Stephen J. Nicholas M.D.**

Executive Producer • **Anthony Loera**

Creative Consultant • **Sean Farrell**

Associate Producer • **Terri Needham and Judy McDowell**

Original Cartoons • **Kate Pappas**

Editor • **Robert Kane Pappas**

Assistant Editor • **Eric Glandbard**

Camera • **Robert Kane Pappas**

Additional Camera • **Eva Dorrepaal and Sam Spade**

Original Music • **Spider Barbour • Paul Groueff**

Narration • **Robert Kane Pappas**

Publicity • **Falco ink.**

In-house Publicity • **Indira Gumarova**

Sill Photography • **Kerri Stallone**