

**“Time is the river which carries me
away, but I am that river;
time is the tiger that devours me,
but I am that tiger”**

J. L. Borges, *Labyrinths*, 1970

5th EMBL/EMBO Conference
on Science and Society

Time & Aging: Mechanisms and Meanings

November 5-6, 2004

European Molecular Biology Laboratory, Heidelberg

Organising Committee:

Halldór Stefánsson (*EMBL, Chair*)

Fotis C. Kafatos (*EMBL*)

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Biological clocks and rhythms are the objects of intensive scientific research of profound interest. Several “clocks” that operate at different levels regulate our relations to the natural and social dimensions of our existence.

First to note is the clock of natural selection, whose irregular ticks mark the birth of new species, separated from one another by intervals of millions of years. The second clock, a product of the first, is that of genetic control, whose exquisitely coordinated rhythm in turning genes on or off accounts for the developmental processes of living organisms. The identities and functions of cells and tissues are defined not simply by what genes they express, but also by when they are expressed and in what order. Our biological integrity is assembled and established by such integrated rhythms and timing. Even shorter periods are represented by the diurnal rhythms which impact much of our metabolism and behavior— sleeping cycles are but one example.

But the biological impact of time refers both to cyclical and to linear mechanisms, which together translate into the complex processes of physical aging. It can be assumed that enhanced understanding of diverse biological master clocks and progressive changes will increasingly bring the dimension of time and aging to the forefront of our appreciation of health and disease.

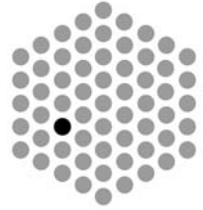
New knowledge and technologies growing out of biological research on “time and aging” are likely to have monumental impact on the quality (and possibly the length) of the human lifespan in future societies. Therefore, this topic is of interest not only for specialised researchers, but also for society at large.

The aim of the joint EMBL/EMBO conferences is to promote interaction and mutual enlightenment between scientists and a wide range of other members of society – all those who are interested in discussing the social impact and relevance of research and applications at the forefront of molecular biology.

Fotis C. Kafatos
Director-General of EMBL

Frank Gannon
Executive Director of EMBO

EMBL



The European Molecular Biology Laboratory (EMBL) is a basic research institute funded by 17 member states, including most of the EU, Switzerland and Israel. Research at EMBL is conducted by approximately 80 independent groups covering the spectrum of molecular biology. The Laboratory has five units: the main Laboratory in Heidelberg, Outstations in Hinxton (the European Bioinformatics Institute), Grenoble (on the campus of ILL and ESRF), Hamburg (on the DESY site) and Monterotondo (sharing a campus with EMMA and the CNR).

EMBL was founded with a four-fold mission: to conduct basic research in molecular biology, to provide essential services to scientists in its Member States, to provide high-level training to its staff, students, and visitors, and to develop new instrumentation for biological research. Over its 30-year history, the Laboratory has had a deep impact on European science in all of these areas. EMBL has achieved so much because it is a truly international, European institution, because it has achieved a critical mass of services and facilities which are driven by cutting-edge biological research, and because it regards education – at all levels – as a way of life.

In 1998, EMBL launched a Science and Society initiative among researchers and staff members to promote awareness of the impact that work within the life-sciences is having on society. The initiative offers events and activities dealing with subjects and themes relevant to the ways in which recent developments within the life sciences in general, and within molecular biology in particular, are having a profound impact on people, their societies as well as their cultures. More information can be found at the EMBL Science and Society website <http://www.embl.org/aboutus/sciencesociety>.



EMBO was founded in 1964 by European scientists at the forefront of the molecular study of biological entities. Its mission is to promote molecular biology in Europe and neighbouring countries.

Today EMBO has 1,200 members, mainly academic scientists, in all fields of molecular biology. The core EMBO activities consist of long-term fellowships for postdoctoral scientists, short-term training fellowships, and courses and workshops in the latest results and methods in molecular biology. More recently, Science & Society and a programme of support for young group leaders have also been added to the general programme. These activities are funded through contributions from the Member States (presently 24) of the EMBC (European Molecular Biology Conference). EMBO also runs programmes and projects supporting the mobility of researchers within and to Europe (World Programme and Life Science Mobility Portal), and a sophisticated search portal for scientific literature (E-Biosci).

EMBO reports, a relatively new publication, complements the established and respected *The EMBO Journal*, hosting not only excellent scientific articles, reviews and meeting reports, but also a large section on Science & Society and science politics and policy. In general terms, EMBO plays an increasingly large role in policy making at the European level, having driven discussions on the soon to be established European Research Council, and played a pivotal role in supporting the European Commission in this area. EMBO's Science & Society Programme, the co-organiser of this conference, develops and organises resources and events that directly or indirectly support the communication of the scientific community with the public, media and policy makers. From international practical workshops for science teachers to the EMBO Award for Communication in the Life Sciences, the programme helps to create a balanced public dialogue on molecular biology and its applications.

More information on EMBO and the Science & Society Programme is available at <http://www.embo.org/projects/scisoc/index.html>.

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programme

Friday, 5 November, 2004

8:00-8:45 Registration
8:45-9:00 Welcome Address: Fotis C. Kafatos (Director-General, EMBL)

Session I: Biology of Time and Aging: State of the Art

Chair: Roland Prinzinger (University of Frankfurt, Germany)
9:00-9:45 Tom Kirkwood (University of Newcastle-upon-Tyne, UK)
Times of Our Lives: What Controls the Length of Life?
9:45-10:30 Ueli Schibler (University of Geneva, Switzerland)
The Time Measuring Systems of Cells and Organisms
10:30-11:00 *Coffee break*
11:00-11:45 Mario Capecchi (University of Utah, USA)
Use of the Mouse to Study Human Longevity
11:45-13:00 *Lunch*

Session II: Relevance and Future Prospects

Chair: Nadia Rosenthal (EMBL-Monterotondo, Italy)
13:00-13:45 Aubrey de Grey (University of Cambridge, UK)
The Foreseeability of Real Anti-Aging Medicine
13:45-14:30 Peter Krammer (DKFZ, Germany)
No Life Without Death
14:30-15:15 Jay Olhansky (University of Illinois, USA)
Will Human Life Expectancy Decline in the 21st Century?
15:15-15:45 Presentation of the EMBO Award for Communication in the Life Sciences
15:45-16:15 *Coffee Break*

Panel Discussion

- Chair: Andreas Kruse (Heidelberg University, Germany)
- 16:15-18:15 Cecil Helman (Brunel University, UK)
Denis Duboule (University of Geneva, Switzerland)
Paul Baltes (Max-Planck-Institut for Human Development, Germany)
Anthony Dick Ho (Heidelberg University, Germany)
Lloyd Demetrius (Harvard University, USA)
- 19:00 *Conference Banquet*

Saturday, 6 November, 2004

Session III: Science and the Industry of Anti-Aging

- Chair: Laura Helmuth (Smithsonian Magazine, USA)
- 9:00-9:35 Charles McConnel (University of Texas, USA)
The Anti-Aging Economy: Prospects and Problems
- 9:35-10:10 Suresh Rattan (University of Aarhus, Denmark)
Aging Intervention: Prevention or Therapy?
- 10:10-10:40 *Coffee Break*
- 10:40-11:15 Paolo Giacomoni (Estée Lauder Companies, USA)
Aging, Industry and Policies: The Cosmetic Point of View
- 11:15-11:50 Kári Stefánsson (deCODE Genetics, Iceland)
Genetics of Longevity in Iceland
- 11:50-13:30 Lunch (Projection of a film by J-F Brunet: "The Life and Times of Life and Times")

Session IV: Transcendence or Transgressions?

- Chair: Geoff Watts (BBC, UK)
- 13:30-14:15 Alex Mauron (University of Geneva, Switzerland)
The Choosy Reaper: From the Myth of Eternal Youth to the Reality of Unequal Death

- 14:15-15:00 Arthur Caplan (University of Pennsylvania, USA)
Is There Anything Immoral About Wanting to Live Forever?
- 15:00-15:45 Debhora Battaglia (Mount Holyoke College, Massachusetts, USA)
A Futurology of Science and Religion: Immortality Reimagined
- 15:45-16:15 *Coffee Break*

Panel Discussion

- Chair: Geoff Watts (BBC, UK)
- 16:15-17:45 Gary Ruvkun (Harvard Medical School, USA)
Karin Knorr Cetina (University of Constance, Germany)
Donald Bruce (Church of Scotland, UK)
- 17:45-18:00 Closing Remarks: Frank Gannon (Executive Director, EMBO)



Session I:

Biology of Time and Aging: State of the Art

Our life span is restricted. Everyone knows this and everyone accepts this as “biologically” obvious, though for most of us this life seems to be too short. “Nothing lives forever.” However, in this statement we think of artificially produced, technical objects; products which are subjected to natural wear and tear during use. This wear and tear leads to the result that at some time or other the object stops working and becomes unusable (“death” in the biological sense). But are the wear and tear and loss of function of technical objects and the death of living organisms really comparable or even similar?

An organism possesses many mechanisms for repair. It is not in principle necessary that a biological system should age and die. Nevertheless a restricted life span, aging and then death are basic characteristics of life. The reason for this is easy to recognize: in nature the existent organisms are regularly replaced by new types. Because of changes in the genetic material (mutations) these organisms have new characteristics and in the course of their individual lives they are tested for optimal or even better adaptation to environmental conditions. Immortality would disturb this system – it needs room for new and better life. This is one basic problem of evolution. Thus death is a basic precondition for the frictionless and rapid development towards better adaptation to the dominant environmental conditions. The restriction of life by death is then sensibly not left to chance, such as disease or accident. It is thus evidently an inherent property of the system of the organism from the first moment of its development. Life span and death are thus programmed from the start of life. This is known as the hypothesis of genetically programmed aging, ending in death, and is not particularly controversial among scientists. The theory does not necessarily posit aging in the sense of slow loss of function before death. Many organisms even die at the zenith of their physiological abilities. For example, many sorts of plant die shortly after flowering and many insects, fish and worms and other animals immediately after reproduction. This is a particularly clear

demonstration of the programmatic character of death. The rare “Progeria”, a hereditary human disease which leads to premature aging, is a further very clear demonstration of the genetic basis of the aging process.

If life span is a genetically determined biological characteristic it is logically necessary to propose the existence of an internal clock, which in some way measures and controls the aging process and which finally determines death as the last step in a fixed programme. This last step can of course consist of a long succession of different ontogenetic processes. It is of great interest to investigate the site and the function of the “clock” for life span and on the question of the unit and the beat in which this clock “ticks”. Are these ticks for example heart beats, breathing acts, metabolic rates or something else? There are a large number of theories dealing with these questions and on the control and the bases of the aging processes *per se*.

– Roland Prinzinger

Session chaired by Roland Prinzinger
Speakers: Tom Kirkwood, Ueli Schibler
and Mario Capecchi



Roland Prinzinger

Chair and Head of Department of Metabolic Physiology, Faculty of Biology, Johann-Wolfgang Goethe University, Frankfurt/Main, Germany

Roland Prinzinger was born on 6 August 1948 in Kirchheim/Teck, Germany. He studied chemistry and biology at the University of Tübingen from 1969-1974, where he received a diploma in biology and his first position as scientific assistant in the Institute of Animal Physiology. In 1984, he moved to Frankfurt/Main where he is the head of the department of Metabolic Physiology in the faculty of biology of the Johann-Wolfgang Goethe University. His main research topics are: Thermoregulation and energetics in animals (especially homeotherms), ornithology, and the theory of aging (what is the clock of our life?). In the field of aging, he mainly worked on the correlation between metabolic rate and life-times (including time duration of embryogeny, post-natal development, etc.). He acted as dean of the faculty from 1997 to 2000, and has been vice- and director of the Institute, treasurer, vice- and president of the German Ornithological Society and is its honorary member; he is national delegate of the Standing Committee of the International Ornithological Congress, corresponding member of the Swiss Ornithological Society, elected member of the Wissenschaftliche Gesellschaft der Universität Frankfurt/Main. He is (co-) author of the following publications: *Der Schwarzhalstaucher Podiceps nigricollis – NBB 521A*, Ziemsen-Verlag (1979); *Pestizide und Brutbiologie der Vögel*. Kilda-Verlag, (1980); *Stillgewässer-Kataster des Landkreises Ravensburg. Ecol. Birds; Sonderheft* (1988); *Ornithologie. 2. Aufl. – UTB Große Reihe. Ulmer-Verlag* (1990); *Das Geheimnis des Alterns – Die programmierte Lebenszeit bei Mensch, Tier und Pflanze*. Campus-Verlag (1996); *Das Geheimnis der Lebensenergie. Wie wir länger jung und gesund bleiben*. Campus-Verlag (1997); “Avifauna der Stillgewässer des Landkreises Ravensburg. Der Bestand 1998 im Vergleich zu 1985/86.” *Ökol. Vögel (Ecol. Birds)* 21 (1999). He has written more than 210 scientific papers. He was awarded the Forschungspreis des Dachverbandes Deutscher Avifaunisten in 1989, Ornithologenpreis der Deutschen Ornithologen-Gesellschaft in 1994, and Preis der 1882-Sparkasse für exzellente Lehre an der Universität in 2003.

Times of our Lives: What Controls the Length of Life?



Tom Kirkwood

Co-Director of the Institute for Aging and Health,
University of Newcastle-upon-Tyne, UK

The last decades have seen exciting progress in solving one of the greatest puzzles in the life sciences: why do we age and what controls length of life? Evidence points to a modest but significant genetic contribution to human lifespan, explaining about 25 per cent of the variation in longevity within the population. However, the genetic contribution to aging comes about indirectly, not through genes that actively bring about senescence and death but through genes that regulate survival. Our survival mechanisms are outstanding but evolved at a time when extrinsic mortality was much more severe and when reproduction was a much higher priority than being able to live forever. Some of the most important genetic factors are indeed proving to be those that involve trade-offs, for example, balancing the benefits of increased fertility against increased survival. There are also important interactions between genetic predisposition for a longer or shorter life and environmental or chance factors, which in turn may be influenced by lifestyle or socio-economic circumstances. There is much greater plasticity in the aging process than has hitherto been recognised, and it is this plasticity that underlies, for example, the actions of long-term calorie restriction in extending life span. The urgency of aging research has never been higher and it is therefore fortunate that we can at last anticipate rapid progress in further unravelling not only the genes that influence longevity but also the detailed molecular mechanisms which are at play. The

complexity of aging is such that the scale of the task should not be underestimated. In an age of science when increasingly we are beginning to appreciate the importance of the integrative approach – assembling a composite picture from the many important discoveries that have flowed from highly focused, reductionist techniques – aging can be seen as one where the discipline of “systems biology” has a great deal to contribute. Expectations of life have never been greater; it is essential that science engages directly and realistically with delivering the knowledge base that can support a greater quality of life in old age.

Tom Kirkwood was born on 6 July 1951 in Durban, South Africa. Educated in biology and mathematics at the Universities of Cambridge and Oxford, he worked at the UK National Institute for Medical Research from 1981 until 1993, when he became Britain’s first Professor of Biological Gerontology at the University of Manchester. In 1999, he was appointed Professor of Medicine at the University of Newcastle-upon-Tyne, where he is Co-Director of the Institute for Aging and Health and heads the Department of Gerontology. He has been Chair of the British Society for Research on Aging, Governor and Chair of the Research Advisory Council of the medical research charity “Research into Aging”, and Chair of the UK Foresight Task Force on “Health Care of Older People”. He is author of the award-winning books *Time of Our Lives: the Science of Human Aging and of Chance, Development and Aging*, co-authored with leading US gerontologist Caleb Finch. He gave the BBC Reith Lectures in 2001 on *The End of Age* (also published in book form) and has contributed to numerous television and radio documentaries and discussions about aging. Kirkwood has been actively involved in aging research since 1975. His work on the disposable soma theory, first proposed in 1977, provides an evolutionary explanation of aging that makes testable predictions about cell and molecular mechanisms and the genetic basis of longevity. The current focus of his research group is on testing these ideas, particularly the role of cell stress response and maintenance systems in aging and longevity. The group has a core interest in modelling the complex molecular mechanisms that contribute to aging and has pioneered network models that permit analysis of interactions between different contributing processes. At an experimental level, the group focuses on integrative mechanisms of cell aging and recently identified some of the first clear evidence for intrinsic age-related changes in the functional properties of tissue stem cells. At a population level, the group has shown evidence in human records of a trade-off between fertility and longevity, as predicted by the disposable soma theory, and has developed evolutionary models to explain menopause in humans and the life-extending effects of calorie restriction in rodents.

The Time Measuring Systems of Cells and Organisms



Ueli Schibler

Professor, Department of Molecular Biology,
University of Geneva, Geneva, Switzerland

Many biochemical and physiological processes fluctuate in a temporal fashion. Cycles with a period length (t) of approximately 24 hours are considered to be circadian, while rhythms with substantially shorter and longer period lengths are called ultradian and infradian, respectively. Virtually all light-sensitive organisms – from cyanobacteria to humans – contain circadian oscillators, and in mammals most vital processes are subject to circadian variations. Thus sleep-wake cycles, locomotor activity, heartbeat, blood pressure, renal plasma flow, body temperature, sensorial perception, and the secretion of many hormones fluctuate during the day in an orderly fashion. The mammalian master circadian pacemaker resides in the suprachiasmatic nucleus (SCN) at the base of the brain's hypothalamus. The phase of this SCN clock is reset every day via the retino-hypothalamic tract, which transmits light information from the retina directly to SCN neurons. Circadian pacemakers were originally believed to exist only in a few specialized cell types, such as SCN neurons. However, in recent years, this view has been challenged by the discovery that circadian clocks exist in most peripheral cell types, even in immortalized tissue culture cells. As feeding time is the major *Zeitgeber* for peripheral clock, the SCN may synchronize peripheral oscillators mostly by driving rest-activity cycles, which in turn determine feeding time. On the molecular level, circadian oscillations are generated by interconnected feedback

loops in gene expression, involving the transcriptional repressors CRY1, CRY2, PER1, PER2, and REV-ERB α , the transcriptional activators CLOCK and BMAL1, and several protein kinases (e.g. protein kinase 1 ϵ). The molecular clock drives the cyclic accumulation and/or activity of downstream regulators, which in turn govern the rhythmic expression of enzymes and thus circadian physiology. One family of such downstream regulators will be discussed in detail.

Ueli Schibler was born in 1947 in Olten, Switzerland, studied biology at the University of Bern and obtained his Ph.D. in 1975. During his thesis project, he compared the secondary structure of pre-ribosomal and ribosomal RNA during vertebrate evolution. From 1975-78 Schibler worked as a postdoctoral fellow on mRNA 5'-capping and immunoglobulin mRNA processing in Robert Perry's laboratory at the Fox Chase Cancer Center in Philadelphia. He then joined the Swiss Institute for Experimental Cancer Research (ISREC), first as a junior group leader (1978-81) and then as a senior group leader with tenure (1981-1984). At ISREC, he investigated the tissue-specific expression of alpha-amylase genes in collaboration with Otto Hagenbuechle and Peter Wellauer. These studies resulted in the discovery of alternative promoter usage and differential splicing. In 1984, Schibler joined the Department of Molecular Biology at the University of Geneva as a full professor. His Geneva research team developed a tissue-specific *in vitro* transcription system using nuclear proteins from solid rat tissues. This simple biochemical assay system allowed the rapid identification of cis-acting elements of model genes and their trans-acting cognate transcription factors. One of these transcriptional regulatory proteins, DBP, was found to be expressed in a strongly circadian fashion in the liver. This unexpected finding motivated Schibler and his coworkers to study circadian clocks in peripheral tissues. Recently, they showed that even cultured fibroblast cell lines contain cell-autonomous and self-sustained circadian oscillators. Schibler is a member of several scientific associations, including EMBO, European Academy of Sciences, Swiss Academy of Medical Sciences, Faculty of 1000, and Union of Swiss Societies in Experimental Biology. He received the Friedrich Miescher Award of the Swiss Biochemical Society in 1983, the Cloëtta Prize for Medicine in 1986, the Otto Naegeli Prize for Medicine in 1996, and the Louis Jeantet Prize for Medicine in 2000.

Use of the Mouse to Study Human Longevity



Mario Capecchi

Professor of Human Genetics, University of Utah,
School of Medicine, Salt Lake City, USA

Gene targeting provides the means for creating strains of mice with designed alteration in any chosen genetic locus. This technology permits the evaluation of the functions of genes in the intact mammal and the systematic dissection of the most complex biological processes from embryogenesis to aging. With virtually complete control over how a gene's DNA sequence is modified, the investigator can disrupt the gene in the germline, and as a consequence, every cell of the mouse carries the disrupted gene, or the modification can be implemented conditionally, thereby restricting the function of the gene in chosen tissues and/or temporal periods of the animal, including adulthood.

Of all of the model organisms, the mouse's genome and physiology is most similar to ours, so it would appear that this creature is likely to be the most informative experimental organism to evaluate the multiple facets that affect the process of aging and permit evaluation of the genetic and environmental factors that most significantly alter the aging process. Is it reasonable to anticipate that the lifespan of the laboratory mouse can be significantly changed through genetic manipulations? Comparisons among the life spans of different mammalian species of comparable size and physiology suggest that it should be. For example, the average life span of the laboratory mouse is approximately two years. However, the microbat species *Myotis lucifugus* readily attains a life expectancy of thirty years. These two species are nearly identical in size and have very similar physiological parameters such as heart rates, blood pressure, body temperatures and metabolic rates. It is not unreasonable to assume that

such enormous differences in life expectancies between these two species is determined in part by genetic differences. We will explore technologies that use the mouse as a surrogate and may allow the identification of such genetic determinants.

Mario R. Capecchi was born in Verona, Italy, in 1937. He received his B.S. in chemistry and physics from Antioch College in 1961 and his Ph.D. in biophysics from Harvard University in 1967. He completed his thesis work under the guidance of Dr. James D. Watson. From 1967-69 he was a Junior Fellow of the Society of Fellows at Harvard University. In 1969, he became an Assistant Professor in the Department of Biochemistry, Harvard School of Medicine, and was promoted to Associate Professor in 1971. In 1973, he joined the faculty at the University of Utah as a Professor of Biology. Since 1988, Dr. Capecchi has been an investigator at the Howard Hughes Medical Institute; since 1989, a Professor of Human Genetics at the University of Utah School of Medicine; and since 1993, Distinguished Professor of Human Genetics and Biology. He is also co-chairman of the Department of Human Genetics. Dr. Capecchi is best known for pioneering the technology of gene targeting in mouse embryo-derived stem cells that allows scientists to create mice with mutations in any desired gene by choosing which gene to mutate and how to mutate it. This gives the investigator virtually complete freedom in manipulating the DNA sequences in the genome of living mice, and allows detailed evaluation of any gene's function during its development or post-developmental phase. Research interests include the molecular genetic analysis of early mouse development, neural development in mammals, production of murine models of human genetic diseases, cancer and factors affecting life expectancy, homologous recombination and programmed genomic rearrangements in the mouse. Dr. Capecchi is a member of the National Academy of Sciences (1991) and the European Academy of Sciences (2002). His prestigious awards include the Bristol-Myers Squibb Award (1992), Gairdner Foundation International Award (1993), General Motors Corporation's Alfred P. Sloan Jr. Prize (1994), German Molecular Bioanalytics Prize (1996), Kyoto Prize in Basic Sciences (1996), Baxter Award for Distinguished Research in the Biomedical Sciences (1998), Colby Presidential Endowed Chair (1999), Italian Premio Phoenix-Anni Verdi Award (2000), Spanish Jiménez-Díaz Prize (2001), Albert Lasker Award (2001), National Medal of Science (2001), John Scott Medal Award (2002), Massry Prize (2002), Pezcoller Foundation-AACR International Award for Cancer Research (2003) and Wolf Prize in Medicine (2002/03).



Session II:

Relevance and Future Prospects

If aging is a universal phenomenon, the expansion of human life expectancy among populations in the industrial world that characterized the twentieth century is unique in the history of humanity. As the extension of human lifespan is projected to continue to rise in the twenty-first century, it may well bring about further revolutionary changes through improvements in medicine and applications of emerging technologies presently brewing within the life sciences. In view of these prospects it is extremely important to promote multi-disciplinary dialogue among experts on the causes, characteristics and consequences of increased human longevity, and to involve the public in reflections regarding its implications. What is the status of our present-day knowledge about the nature of aging, at the molecular, the cellular, and the organismic level? Can it be applied any time soon to fight the plight of age-related degenerative diseases, to improve the quality of the human lifespan? How is it likely to impact on the future on people's life expectancy and the population profiles of their societies? Since those of us who live in the industrial world are already faced with a radical aging of the human population, how will we deal with a further intensification of that trend and what are its possible repercussions?

Session chaired by Nadia Rosenthal
Speakers: Aubrey de Grey, Peter Kramer
and Jay Olshansky



Nadia Rosenthal

Head of the Mouse Biology Program EMBL
Monterotondo, Rome, Italy

Professor Nadia Rosenthal is Head of the European Molecular Biology Laboratory's Outstation in Monterotondo (Rome), Italy. She moved to EMBL in 2001 from Harvard Medical School, where she directed a biomedical research laboratory at the Massachusetts General Hospital and served as an editor at the *New England Journal of Medicine*. Professor Rosenthal is a member of EMBO, and has been awarded the Ferrari-Soave Prize in Cell Biology. She has served on numerous grant review committees, advisory panels and editorial boards and is a member of the European Group on Life Sciences. She currently holds a visiting Professorship at the University of Western Australia. Professor Rosenthal's laboratory has a strong interest in developmental genetics of skeletal muscle and heart with a parallel focus in the molecular biology of aging and stem cell-mediated regeneration.

The Foreseeability of Real Anti-Aging Medicine



Aubrey de Grey

Research Associate, Department of Genetics,
University of Cambridge, UK

Unlike most of society, biogerontologists are generally keen to see aging combated as thoroughly as soon as possible. When it comes to translating that view into effective action, however, our record is not impressive. Prominent biogerontologists enjoy exposure in national media that only a tiny minority of other scientists can attract, yet the insatiable public interest in our research has not resulted in comparable public funding. This may largely be due to our reluctance to reconsider a presentational policy that has failed us for 50 years (namely, emphasis on the biomedical pipe-dream termed “compression of morbidity” and pretence that our work holds no “risk” of extreme life extension). Recently we have been committing an even more inexcusable failure, lamentably common in science but no less reprehensible for that: to critique in public, in detail, each other’s ideas for combating aging. Only by surviving such scrutiny will any of our proposals achieve enough credibility to attract the funds needed to realise them, so this reticence hurts us all. It prevails for the obvious reasons: successfully challenging one’s colleagues’ views risks revenge next time they review one’s grant application, and doing so unsuccessfully exposes one’s own ignorance or carelessness. Silence, by contrast, allows one’s views to persist unchallenged indefinitely, which increasingly transforms them from objective opinions into articles of dogmatic faith. Biogerontology is perhaps the field in which this is most reprehensible, given the mind-numbing scale of the deaths for which aging (and, thus, any delay in combating aging) is responsible. Put simply, to place careerist or egoist considerations ahead of our duty to expedite healthy life-extending interventions is an act of self-serving folly that society will not easily forgive when success finally arrives. The greatest absolute

life extension hitherto achieved in different species by caloric restriction (CR) or related methods is almost independent of their control lifespan. This fact starkly undermines the currently fashionable extrapolation from rodent CR to predictions of a ~20-year human life extension from foreseeable CR-emulating drugs, and instead predicts a maximum benefit of only 2-3 years – as I have recently argued in depth, in print. My detailed proposal – now four years old – to combat aging not by the “holistic” approach exemplified by CR, but instead by taking aging apart and repairing each type of cellular or molecular “damage” independently, has not been reciprocally critiqued, even though several prominent colleagues have publicly endorsed it. I contend that we have an urgent and overwhelming duty to set aside our egos and debate the feasibility of specific approaches to the combating of humanity’s foremost remaining scourge.

Aubrey de Grey was born on 20 April 1963 in London, England. He obtained his undergraduate degree in computer science and his Ph.D. in gerontology, both from the University of Cambridge, where he still works. Dr. de Grey is the Editor-in-Chief of *Rejuvenation Research*, the world’s only peer-reviewed journal focused specifically on reversal (repair) of the molecular and cellular changes that accumulate throughout life and eventually give rise to frailty, disease and death. He is also an associate editor of *Mitochondrion* and the *Journal of Evolution and Technology* and an editorial board member of *AGE*, the journal of the American Aging Association. He serves on the board of directors of the British Society for Research on Aging, the American Aging Association and the International Association of Biomedical Gerontology. His contributions to the field have been recognised by Fellowship of the Gerontological Society of America and by the World Transhumanist Association’s H.G. Wells award for outstanding contributions to transhumanism (the expansion of human potential through technology). Dr. de Grey’s work in gerontology over the past decade has progressed from a traditional theoretician’s role (formulation of new explanations for paradoxical data), through an engineer’s role (the identification of novel biotechnological approaches to the repair of various types of age-related pathogenic damage) to that of a provocateur (critiquing the oversights and dogmatism of the biogerontology establishment). He has published extensively in all these areas, with over 20 first-author papers in peer-reviewed journals in the past eight years. His major interests are the aspects of aging in which existing research falls furthest short of what will be needed for comprehensive repair of age-related damage: mutations in the mitochondrial DNA, indigestible aggregates in the lysosome, and cancer. He also publishes and speaks regularly on the social context of radical life extension and humanity’s duty to hasten it by more intervention-focused research.

No Life Without Death



Peter Krammer

Director of the Tumor Immunology Program,
German Cancer Research Center (DKFZ),
Heidelberg, Germany

CD95, a member of the tumor necrosis factor (TNF) receptor superfamily, induces apoptosis upon receptor oligomerization. The receptor and its ligand are important for apoptosis of peripheral T cells, for downregulation of an immune response and most likely, at least in part, also for peripheral T cell tolerance. In AIDS, apoptosis mediated by this system might contribute to the depletion of T helper lymphocytes. Likewise, in diseases in which liver cells are destroyed, the CD95 system might play a major role. In a search to identify the intracellular signalling pathway of CD95 several molecules coupling to oligomerized CD95 were immunoprecipitated from apoptosis-sensitive human leukemic T cell and lymphoblastoid B cell lines. The following binding molecules were only associated with aggregated and not with monomeric CD95: phosphorylated FADD (MORT1) and caspase 8. Thus, caspase 8 was identified as the most CD95 receptor proximal protease which starts the cascade of protease reactions important for CD95-mediated apoptosis. Association of FADD and caspase 8 with CD95 was not observed with C-terminally truncated non-signalling CD95. FADD and FLICE did also not associate with a CD95 cytoplasmic tail carrying the IPRCG amino acid replacement. FADD and caspase 8 form a death-inducing signalling complex (DISC) with the CD95 receptor and are, thus, the first CD95 associating proteins of a signalling cascade mediating apoptosis. The function of the DISC is discussed in detail, particularly with respect to its role in sensitivity and resistance to apoptosis. The CD95 death system plays a role in destruction of liver tissue. In hepatitis cytotoxic T lymphocytes might use the CD95 system to kill infected hepatocytes. In *M. Wilson* copper overload leads to upregulation of the CD95 ligand that may finally contribute to acute liver failure. In HCC from patients treated with

chemotherapeutic drugs the CD95 receptor and ligand are upregulated and may contribute to apoptosis of the tumor or, depending on the drug sensitivity of the tumor, to the status of the tumor as an immunoprivileged site.

Prof. Dr.med. Peter H. Krammer was born in Rheydt, Rhineland, Germany. He received his medical training in Freiburg, Germany, St. Louis, USA, and Lausanne, Switzerland. He did his thesis on extracellular streptococcus antigens at the Institute for Microbiology and Hygiene at the University of Freiburg, and investigated the role of small nuclear RNAs at the Institute of Pathology, also in Freiburg. In 1973, at the age of 27, he became a member of the Basel Institute for Immunology and spent almost three fruitful years at the Institute studying T cells and their specificity. From Basel, he moved via the Max-Planck-Institute for Immunobiology in Freiburg, where he stayed one year to continue T cells studies, to Heidelberg to the German Cancer Research Center, where in 1976 he started his work in the Division of Immunogenetics. There, again, his main work was on T cells and T cell clones, their receptor specificities and their activities. Later, in the early 1980s, he focused on T cell-derived cytokines. He investigated the activation of macrophages by macrophage activating factors and in a fruitful, longstanding collaboration with E. Vitetta and her associates from Dallas, discovered IL-4 as a B cell immunoglobulin switch factor. With fondness he remembers his days as a visiting professor in Dallas and the friendliness of the Texans who hosted his stay. In 1984/85, he felt that molecular biology would leave a significant mark on immunology and he spent one and a half years in A. Sippel's laboratory at the Center for Molecular Biology in Heidelberg to learn the thinking and the techniques in this field. In the mid-to-late 1980s, his interest shifted very much towards negative regulation of tumor cell growth and apoptosis. In this context he and his associates discovered the CD95(APO-1/Fas) system, highlighted by the first publication in *Science* in 1989. CD95, its signalling machinery and its role in physiology and diseases remained at the center of his interest. Peter Krammer has received numerous prizes for his work and is a reviewer for and serves on the editorial board of many journals. Presently, he is the Director of the Tumor Immunology Program of the German Cancer Research Center. He runs a large group of scientists and his main interest is sensitivity and resistance in apoptosis and the role of apoptosis in the immune system and in diseases.

Will Human Life Expectancy Decline in the 21st Century?



Jay Olshansky

Professor, School of Public Health, University of Illinois, Chicago, USA

Forecasts of human life expectancy are an important component of public policy because they influence the funding for, and solvency of, age-entitlement programs. In the United States the Social Security Administration (SSA) recently decided to raise their estimates of how long Americans are going to live in the 21st century. However, current trends in childhood and adult obesity in the U.S. and other low mortality populations and the global re-emergence of communicable diseases, pose serious threats to the health and longevity of present and future generations. Furthermore, death rates and life expectancy at older ages in the U.S. have remained relatively constant for the past twenty years. In this talk empirical evidence is presented demonstrating the existence of these trends and their possible affect on life expectancy, as well as the public health measures required to mitigate them is discussed. We believe there is sufficient evidence to support the conclusion that unless broad scale public health measures are enacted to address the obesity epidemic and rise of communicable diseases, human life expectancy could decline in the 21st century.

Jay Olshansky received his Ph.D. in Sociology at the University of Chicago in 1984. He is currently a professor in the School of Public Health at the University of Illinois at Chicago and a Research Associate at the University of Chicago's Center on Aging and the London School of Hygiene and Tropical Medicine. Dr. Olshansky was a faculty member of the Department of Medicine at the University of Chicago from 1989 to 2000. The focus of his research to date has been on estimates of the upper limits to human longevity, exploring the health consequences of individual and population aging, and global implications of the re-emergence of infectious and parasitic diseases. During the last ten years, Dr. Olshansky has been working with colleagues in the biological sciences to develop the modern "biodemographic paradigm" of mortality – an effort to understand the biological nature of the dying out process of living organisms. Dr. Olshansky is the recipient of a Special Emphasis Research Career Award (SERCA) and an Independent Scientist Award (ISA) from the National Institute on Aging – awards that were designed to permit him to expand his formal training in the fields of evolutionary biology, molecular biology, genetics, epidemiology, population biology, anthropology, and statistics, as each field relates to aging. Dr. Olshansky is the current president of the Society for the Study of Social Biology, a Senior Fulbright specialist on biodemography, Associate Editor of the *Journal of Gerontology: Biological Sciences and Biogerontology*; on the editorial board of several other scientific journals, and is a member of the American Association for the Advancement of Science, the New York Academy of Sciences, the Gerontological Society of America, and the Population Association of America. Dr. Olshansky is also listed in *Who's Who in Science and Engineering*, *Who's Who in Medicine and Healthcare*, *American Men & Women of Science*, and *Who's Who in the 21st Century*. He has spoken before the President's Council on Bioethics and has testified several times before the trustees of the Social Security Administration where his research has influenced forecasts of life expectancy and the future solvency of the nation's age entitlement programs. Dr. Olshansky has been invited to lecture on aging throughout the world, and has participated in a number of international debates on the future of human health and longevity. He is the lead author of a book entitled *The Quest for Immortality: Science at the Frontiers of Aging* (Norton, 2001).

Panel Discussion

Discussion chaired by Andreas Kruse
Panelists: Cecil Helman, Denis Duboule, Paul Baltes,
Anthony Dick Ho and Lloyd Demetrius



Andreas Kruse

Professor of Psychological Gerontology, University of Heidelberg, Heidelberg, Germany

Born on 26 of August 1955 in Aachen, married to Sylvia Kruse with two children. Study of Psychology, Philosophy and Music at the universities of Aachen and Bonn and the Academy of Music in Cologne. Doctoral thesis in Psychology on "Structures of experience and behavior in chronic diseases" at the University of Bonn, Habilitation in Psychology on "Competence in old age – relationships to objective and subjectively perceived aspects of life situation" at the University of Heidelberg. Foundation director, foundation professor and chair of Lifespan Psychology and Pedagogical Psychology at the Psychological Institute of the University of Greifswald (1993-1997), since 1997 director of the Gerontological Institute and chair of Gerontology of the University of Heidelberg. International and national grants. 1st International Presidential Award of the International Association of Gerontology, Max Bürger Preis of the German Society for Gerontology and Geriatrics, 1st Intergenerational Award of the federal state Rhineland-Palatinate, medical and psychological awards. The Gerontological Institute of the University of Heidelberg is a Collaboration Center of the World Health Organization (Geneva). Guest professorships at the universities of Jerusalem, Copenhagen and Lund. Main research interests: Competence in old age, productive aging, consequences of demographic change, rehabilitation, intervention research, palliative medicine and palliative care, ethical questions. Third-party funds received from European Commission, German Ministry for Science and Technology, German Ministry for Family Affairs, Senior Citizens, Women and Youth, German Ministry for Work and Social Affairs, German Ministry for Health and Social Security, German Research Foundation, Federal Ministry for Science and Arts of Baden Württemberg, Robert Bosch Foundation.



Cecil Helman

Professor of Medical Anthropology, Department of Human Sciences, Brunel University, USA

Cecil Helman was born in 1944 in Cape Town, South Africa. After qualifying as a doctor at University of Cape Town, he did a postgraduate degree in social anthropology at University College London. He is currently Associate Professor of Medical Anthropology in the Department of Human Sciences, Brunel University, and Senior Lecturer in the Department of Primary Care & Population Sciences, Royal Free and University College Medical School. Helman is one of the leading international experts on medical anthropology, cross-cultural health care, and the cultural dimensions of health, illness and medical care. His textbook *Culture, Health and Illness* (4th edition, 2001) is the best-selling text in medical anthropology and in cultural competence in health care, and since 1984 it has been used as a textbook in 39 countries, and in over 120 universities, medical schools and nursing colleges in the USA and Canada. Helman's research work has focused mainly on lay perceptions of illness, cultural concepts of body image, psychosomatic disorders, cultural dimensions of heart disease, doctor-patient communication and the social, cultural and economic context of health, illness and medical care. He has been on the editorial board of several journals, including *Medical Humanities*, *Medical Anthropology Quarterly*, and *Culture, Medicine and Psychiatry*. His papers have been published in the *Lancet*, *British Medical Journal*, *Annals of Internal Medicine*, *Social Science and Medicine*, *British Journal of General Practice*, *Culture, Medicine and Psychiatry*, and other journals. He is a Fellow of the Royal Anthropological Institute, and of the Royal College of General Practitioners. Since 1989 Helman has been involved in several international medical aid programmes, funded by the British Council: the Community Medicine Program, Conceicao Hospital, Porto Alegre, Brazil (1989-1991); the Department of Primary Care, University of Cape Town, South Africa (1997-2000); and the Department of Family Medicine, University of Transkei, South Africa (1997-2004).



Denis Duboule

Professor of Genetics, University of Geneva,
Switzerland

Denis Duboule was born in Geneva, Switzerland in 1955. Educated in biology at the University of Geneva, he worked at the medical school in Strasbourg and at the EMBL, Germany, before becoming Professor of Developmental Biology. He is currently Chairman of the Department of Zoology and Animal Biology in Geneva, and Director of the National Center of Excellence “Frontiers in Genetics”. He is member of several societies, organisations and academies. He is editor of the journal *Development* and has received several national and international prizes, amongst which the Louis-Jeantet prize for Medicine (1998), the Marcel Benoist prize (2003) and the Grand Prix de Biologie Ch.-Léopold Mayer from the French Academy of Sciences (2004). He is actively involved in the communication of science through numerous TV and radio programmes as well as chronicles in newspapers. Duboule’s scientific contributions are in the field of developmental genetics and evolution, in particular the study of the function and regulation of genes involved in vertebrate body patterning. For many years, he has been interested in understanding the molecular mechanisms underlying specific temporal processes at work during development.



Paul Baltes

Director, Max-Planck-Institute for Human Development, Berlin, Germany

Paul Baltes is a senior fellow (Mitglied) of the Max Planck Society for the Advancement of Sciences, director at the Max-Planck-Institute for Human Development in Berlin (Germany), and part-time Distinguished Professor of Psychology at the University of Virginia (USA). His research interests include theories and models of adaptive (successful) human development, interdisciplinary perspectives on gerontology, cognitive aging, and the psychology of wisdom. Currently, he directs the newly created Max Planck International Research Network on Aging (MaxNetAging) in which several organizations collaborate. Baltes is a member of numerous scholarly and academic organizations, including Academia Europaea, the Berlin-Brandenburg Academy of Sciences, the Gerontological Society of America, the International Society for the Study of Behavioral Development, the German Academy of Sciences Leopoldina (Vice-President, 2001-present) the American Academy for the Arts and Sciences, and the Royal Swedish Academy of Sciences. His numerous awards include the International Psychology Award of the American Psychological Association, the Aristotle Prize of the European Federation of Psychological Associations, the Novartis Prize for Gerontological Research of the International Association of Gerontology, the Robert W. Kleemeier award in recognition of outstanding research in the field of gerontology of the Gerontological Society of America, the Ipsen Foundation Longevity Award, the Lifetime Achievement Award of the German Society of Psychology, and honorary doctorates from the University of Jyväskylä (Finland), the University of Stockholm (Sweden), the University of Geneva (Switzerland), and Humboldt University (Germany). After receiving his doctorate in 1967 from the University of Saarland (Germany), Baltes spent 12 years as a faculty member and department head in the United States. In 1977-78, 1990-91, and 1997-98, he was a Fellow at the Stanford Center for Advanced Study in the Behavioral Sciences.



Anthony Dick Ho

Professor, Chair of the Department of Medicine V,
Heidelberg University, Heidelberg, Germany

Prof. Dr. med. Anthony D. Ho has been Chair of the Department of Medicine V (Hematology, Medical Oncology and Rheumatology) of the University of Heidelberg since April 1998. He attended Medical School at the University of Innsbruck, Austria, and at the Ruprecht-Karls-University of Heidelberg and graduated in 1974. Thereafter he received training in internal medicine, hematology and medical oncology at the Medical Center of the University of Heidelberg. In 1990 he accepted a position as Full Professor at the University of Ottawa, Canada, and founded a cancer research center and a bone marrow transplant unit at the Northeastern Ontario Regional Cancer Center, Sudbury, Ontario, Canada. Accepting an offer as Professor of Medicine at the University of California, San Diego (UCSD), he relocated to San Diego in 1992. Subsequently he was appointed Co-division Chief of Hematology-Oncology at UCSD from 1994-1998. His tenure at UCSD ended in April 1998 when as he accepted his present position as Chair of the Department of Medicine V in Heidelberg. His focus of research has been the behavior and biology of marrow derived stem cells and their applications in clinical transplantation. He has built up blood stem cell transplantation units at University of Heidelberg, the Cancer Center in Sudbury and at UCSD. He is a member of the Heidelberg Academy of Sciences, and the National Ethics Commission for Stem Cell Research of Robert-Koch Institute, Berlin. He received the title of Honorary Professor from the Tongji Medical University in Wuhan, China, in October 2003.

Lloyd Demetrius

Research Scholar, Harvard University
Harvard University , Department of Organismic
and Evolutionary Biology

Education: Undergraduate Studies (Mathematics) – University of Cambridge, England. B.A; M.A (1964); Graduate Studies (Mathematical Biology) – University of Chicago, Ph.D (1968), Post doctoral Studies (Applied Mathematics) – University of Berkeley, Berkeley, California

Current Affiliation: Harvard University, Department of Organismic and Evolutionary Biology (Research Scholar, since 1995) and Max Planck Institute for Molecular Genetics (Research Scientist, since 2002)

Previous Affiliation (Selected list): Harvard University, Massachusetts Institute of Technology (MIT), University of Grenoble, University of Paris (Visiting Professorships) Max Planck Institute for Biophysical Chemistry, Goettingen (Research Scientist)

Awards: Humboldt Fellowship; Guggenheim Fellowship.; Chaire Municipal, University of Grenoble, EMBO fellowship.

Research Interests: Computational Biology, Mathematical Studies of Evolutionary Processes. Systems Biology

Recent Publications – selected list: “Caloric Restriction, metabolic rate and entropy”, *Jour. Gerontology. Biological Sciences*, 2004; “Complexity and demographic stability in population models” (with M. Gundlach and G. Ochs), *Theor. Population Biology*, 2004; *Quantum Statistics and Allometric relations in Biology*, *Physica A*, 2003



Session III:

Science and the Industry of Anti-aging

Popular culture everywhere abounds in an amalgam of old and new remedies for aging and longevity. Its advocates expound miraculous healing powers and life-enhancing properties of a large variety of foods, waters, vitamins, minerals, hormones, chemicals, and spiritual practices that they offer to us as easily attainable commodities of the free market. Various sorts of medical professionals throughout the world successfully advocate the idea that ways and means to slow down, stop, or reverse the aging process are available. As such, anti-aging is a well-established multi-billion dollar biomedical and cosmeceutical business sector. In recent years, research scientists have increasingly started to lay claims to their specific knowledge (and, possibly, mastery) of the biological mechanisms of aging. What motivates scientists in their choice of research topics is evidently a complex question. Socioeconomic and historical circumstances often work together to attract researchers and cluster them around certain areas of inquiry and to abandon other. Why, then, would life scientists start to get interested in the study of “aging”? Life scientists claim that progress within molecular and cell biology has opened the door to an approach fundamentally different from the age-old folk traditions of anti-aging. Discovering the rules that govern life at the molecular level, they say, will allow people to exert direct control over specific genes for the first time in history. This technology has the potential to enhance health and extend longevity by allowing us to augment gene products that diminish with age; to suppress the action of harmful genes; to remove damaged or harmful genes and replace them with desirable ones; to amplify the action of genes that enhance health and longevity; and to predict which individuals are at risk for genetic diseases.

Session chaired by Laura Helmuth

Speakers: Charles McConnel, Suresh Rattan, Paolo
Giacomini and Kári Stefánsson



Laura Helmuth

Science Editor, *Smithsonian Magazine*,
Washington, USA

Laura Helmuth is the science editor for *Smithsonian Magazine*, a general-interest monthly magazine with about 8 million readers. She previously served as an editor for *Science's* news department, where she handled stories about aging, neuroscience, molecular biology, and other life sciences. She currently writes and edits as a freelancer for SAGE-KE, the Science of Aging Knowledge Environment produced by the American Association for the Advancement of Science. Helmuth earned a Ph.D. in cognitive neuroscience in 1997 at the University of California, Berkeley. She conducted part of her dissertation research in Tübingen, Germany, on a DAAD fellowship.

The Anti-Aging Economy: Prospects and Problems



Charles McConnel

Professor of Health Care Sciences, University of Texas, Dallas, USA

Although anti-aging medicine is rarely defined, from an economic perspective it appears to encompass at least three relatively diverse areas of activity: 1) the production and marketing of a broad assortment of life-enhancing products, services and devices, many promoted and intended principally for an aging population, 2) highly technical research programs in firms launched by entrepreneurial scientists whose main objectives include expansion of the life-span through manipulation of the human genome and, 3) on the boundary of the antiaging concept, a sub-sector of the biotechnology industry producing pharmacogenomic advances in genetic testing and therapy targeted toward identifying the genetic determinants of disease and interventions that directly affect the quality and quantity of life. Each of these diverse areas currently or potentially must compete for economic resources and markets within a traditional but highly progressive medical technology sector, is constrained by uncertainties similar to those that impinge on the provision and consumption of conventional health services and is driven by a similar technological imperative. Given the constraints and opportunity costs associated with the production and consumption of anti-aging products and services, health economics offer a clear conceptual and theoretical framework within which the potential behavior of economic agents, be they consumers or producers, can be evaluated and outcomes better anticipated. The health production model, which incorporates disease as a random event and views the consumer of health care as one who is investing in additional productive days of life as well as in the enjoyment of

those additional days, seems appropriate since it accommodates investments in both the quantity and quality of life. This presentation will examine the relevance of several economic concepts to anti-aging medicine including the economic value of additional years of life, time value of money and recent application of cost-effectiveness analysis to biogenetic testing and the adoption of biogenomic products.

Dr. McConnel is a Professor of Health Care Sciences in the University of Texas Southwestern School of Allied Health Sciences, an Associate Professor of Family Practice and Community Medicine in Southwestern Medical School in Dallas and an Adjunct Professor of Management and Policy Science in the University of Texas School of Public Health, University of Texas Health Sciences Center at Houston. Prior to his appointments in the U.T. system, Dr. McConnel taught at San Diego State University, Alfred University, Occidental College and the University of Southern California. Dr. McConnel teaches courses in health care economics, epidemiology of aging, statistics and economics of aging. His research has included studies of the economics of long-term care and survival patterns of institutionalized patients, economic factors in the geographical distribution of physicians and health services utilization by the rural elderly. He has been the Principal Investigator on research grants funded by the National Center for Health Services Research (now Agency of Healthcare Research and Quality), National Institute on Aging, Health Care Financing Administration, the Andrus Foundation (AARP) and the Hogg Foundation. His most recent work has focused on the socio-demographic determinants of demand for prehospital emergency services and health expenditure patterns of the elderly. In addition to his teaching and research, Dr. McConnel has conducted studies for the university on the economic impact of the medical school on the regional economy and studies for the Executive Vice-Chancellor for Health Affairs, University of Texas System, on the economic impact of all U. T. medical schools on the state economy. Other professional activities include past membership on the Texas Department of Health's Osteoporosis Advisory Committee, and a member of the Steering Committee of the Dallas County Coalition on Aging and Developmental Disabilities and Technical Advisory and Investment Panels of the United Way of Metropolitan Dallas.

Aging Intervention: Prevention or Therapy?



Suresh Rattan

Professor of Biogerontology, University of Århus,
Århus, Denmark

Biogerontologists are now in a position to construct general principles of aging and explore various possibilities of gerontomodulation using rational approaches. While not giving serious consideration to the claims made by charlatans, it should be recognized that several scientists are making genuine efforts to test and develop means of intervention in the process of aging and of treating age-related diseases. Whereas more effective, affordable and accessible treatments for diseases are urgently required, the focus of “anti-aging” research is now shifting towards finding ways of slowing down or modifying the basic process of aging, which is the common cause behind a plethora of age-related diseases. The rationale for this preventive approach is our understanding of aging as a progressive failure of maintenance and repair, especially during the survival period beyond the essential lifespan required from an evolutionary point of view. Some of the means of intervention and prevention that have varying degrees of effectiveness include natural and synthetic antioxidants, hormonal preparations, bioextracts from animal and plant sources, enzyme mimetics and small bioactive molecules. Most commonly, these agents are used as nutritional supplements, nutraceuticals and cosmeceuticals with or without a combination with more drastic measures such as surgical interventions. Another approach, termed hormesis, involves challenging cells and organisms by mild stress that results in beneficial and health promoting effects. For example, in a series of experimental studies, we have reported that repeated mild heat stress has anti-aging hormetic effects on various cellular and biochemical characteristics of human skin fibroblasts undergoing aging *in vitro*.

The beneficial effects of repeated mild heat shock include the maintenance of stress protein profile, reduction in the accumulation of oxidatively and glycoxidatively damaged proteins, stimulation of the proteasomal activities for the degradation of abnormal proteins, improved cellular resistance to oxidative and glycoxidative stress, and enhanced levels of cellular antioxidant ability. Other stresses which, while given at low doses, have been shown to have hormetic beneficial effects on the survival and longevity of various experimental organisms include irradiation, pro-oxidants, hypergravity, ethanol and food restriction. Human applications of hormesis include early intervention and modulation of the aging process for preventing and/or delaying the onset of age-related conditions, such as sarcopenia, Alzheimer's disease, Parkinson's disease, cataracts and osteoporosis.

Suresh Rattan, PhD, DSc, is a Research Professor of Biogerontology, at the Danish Centre for Molecular Gerontology, University of Århus, Denmark. His original research and areas of expertise include human cellular aging, gerontogenes, and aging intervention, prevention and therapies, including modulation through growth factors and mild stress (hormesis). He is the founding Editor-in-Chief of *Biogerontology*, a peer-reviewed international journal on the biology of aging. He has published over 150 articles and several books, including those for school children, general public and research scientists. Some of his research has demonstrated the anti-aging effects of kinetin, which is now a component of several anti-aging skin care products on the market.

Aging, Industry and Policies: The Cosmetic Point of View



Paolo Giacomoni

Executive Director-R&D, Clinique Laboratories,
New York, USA

The reverse pyramid of ages in western populations has generated a market for products directed to accompany the aging baby-boomers. Besides geronto-medicine, a vast sector of consumers orient themselves towards nutritionals, sports, clothing, fashion, and cosmetics designed to meet the needs of the graying population. Skin aging is characterized by wrinkling, sagging, thinning and discoloration. The micro-inflammatory model of skin aging predicts the first three phenomena, and fails to predict the fourth one. Aging is defined as the accumulation of damages, and treatments able to reduce the rate of accumulation of damages can be thought of as anti-aging treatments. Strategies to avoid excessive exposure to solar ultraviolet radiation are but one example of successful treatments to slow down the rate of accumulation of damages in the skin and therefore to fight skin aging. Sunscreens are a tool used against ultraviolet radiation. The industry produces sunscreens designed and selected to be photo-stable with high molar extinction coefficients, non photo-toxic, non-allergising, odorless, and colorless. The alliance between industry and science has fostered great progress in photobiology. Legislation has set rules which differ in different parts of the globe: there are sunscreens accepted in the EU which are not allowed in the US, sunscreens accepted in the US which are forbidden in Europe. In Japan, the Ministry of Health requires that new products such as preservatives or sunscreens be tested on animals, whereas in Europe legislation imposes a ban on animal testing for cosmetics. Paradoxically, testing

to assess safety in humans will have to be performed with alternative methods (i.e. not on animals) whereas new molecules will have to be tested on animals to be proven environmentally friendly. The cosmetic industry is complying with the regulatory requirements.

Paolo U. Giacomoni received a Laurea in Atomic Physics from the University of Milan and a Ph.D. in Biochemistry from the University of Paris. He was a teacher at the University of Paris, and was a fellow scientist at University of California, San Diego, at the University of Wisconsin, Madison and at the Deutsches Krebsforschungszentrum in Heidelberg. He is Executive Director-R&D, at Clinique Laboratories, Inc. in Melville, NY. He discovered that UV radiation elicits heat shock response and cell blebbing, and impairs energy metabolism in the epidermis. He worked on the pro-oxidative behavior of UVA radiation and discovered that DNA damage by UVA requires oxygen and transition metals. As consequence, he proposed the now widely accepted micro-inflammatory model of skin aging and his laboratory was one of the twelve laboratories that created the European Union-sponsored Network on Molecular Gerontology. He was among the founders of the European Society for Photobiology and was elected Secretary of the Society for two successive two-year terms.

Genetics of Longevity in Iceland



Kári Stefánsson

President and CEO, deCODE Genetics, Reykjavik, Iceland

In their studies of the genetics of common diseases, scientists at deCODE genetics have collected a formidable amount of both phenotypic and genotypic data on more than 50% of the adult population of Iceland. When these data are analyzed in the context of data on the genealogy of the entire Icelandic nation it provides considerable transparency into the genetics of the lifespan of people. I will discuss the following observations on the genetics of longevity that we have extracted from these data:

1. In Iceland there is considerable genetic component to the risk of becoming more than 90 years of age. The effect of this begins to show once an individual becomes 65 years of age; those who have at least one parent who becomes more than 90 stand a significantly less chance of dying within a year than those with both parents dead at less than 90. Furthermore, the genetic component of longevity appears to be relatively simple.
2. We have mapped to genomewide significance two genes that confer increased risk of longevity in Iceland.
3. In one of the longevity loci we have found an inversion of approximately 0.9 Mb that is significantly associated with longevity in Iceland. Within the inverted segment of DNA there are several genes in which expression is influenced by the orientation of the inverted piece. Variants in one of them have previously been implicated in deterioration of cognitive function.
4. The second longevity locus coincides exactly with a locus that contains a gene

that influences the expression of another gene that contains variants some of which predispose Alzheimer's Disease and others that protect against the same.

Our conclusions are that:

1. The risk of becoming 90 years of age has a genetic component that is significant enough to reach through a long life of environmental influences.
2. The genetic component is simple enough to lend itself to analysis with linkage.
3. It appears that the integrity of the brain is one of the factors that cap our lifespan potential.

Kári Stefánsson has served as President, Chief Executive Officer and Director since he co-founded deCODE in August 1996. Dr. Stefánsson was appointed to serve as the Chairman of the company's Board of Directors in December 1999. From 1993 until April 1997, Dr. Stefánsson was a professor of Neurology, Neuropathology and Neuroscience at Harvard University. In addition, from 1993 through December 1996 he was Director of Neuropathology at Beth Israel Hospital in Boston, Massachusetts. From 1983 to 1993, he held faculty positions in Neurology, Neuropathology and Neurosciences at the University of Chicago. Dr. Stefánsson received his M.D. and Dr.Med. from the University of Iceland.



Session IV:

Transcendence or Transgressions?

What we would like to focus on in this last session is how knowledge and new technologies growing out of research on time/aging may, if they are applied on an industrial scale, end up affecting the quality and the length of the human lifespan. Is there a way to assess the likely impact such future “geronbiotechnology” scenarios would have on people’s perceptions of themselves as members of society as well as individuals? In focusing on different kinds of modern-day life-extension projects associated with anti-aging medicine and “the biology of time/aging” we would like to assess the social and ethical implications of this new enabling knowledge. Will it be beneficial for society, or, inversely, will it bring new areas of risk and inequalities with life-lengthening eugenics becoming the exclusive reserve of those who can afford it? What effect would mastery of biological time/aging have on how identities are socially constituted and sustained? Will increased knowledge of “the biology of time/aging” enable us to distance ourselves from what has hereto been regarded as immutable biological determinants of the life course and its trajectory? What are the possibilities and limits to the malleability of our biological constitution?

Session chaired by Geoff Watts
Speakers: Alex Mauron, Arthur Caplan
and Debora Battaglia



Geoff Watts

Science Editor, BBC, London, UK

G Geoff Watts spent five years in medical research, working on cancer and on the effects of lasers on the eye. But he abandoned an academic career in favour of science and medical journalism. He began in print, and between 1972 and 1980 worked for *World Medicine* magazine – first as science editor and then as deputy editor. It was during this time that he began broadcasting. He has presented countless features and series for BBC Radios 3 and 4 – notably “Science Now” and “Medicine Now”, the latter programme throughout its existence – and for the World Service. He is now the presenter of Radio 4’s science magazine programme “Leading Edge.” He has written books on irritable bowel syndrome and the placebo effect, and contributed chapters to two more on the future of medicine. He divides his time between writing, broadcasting, and media consultancy work. He is also a member of the UK Government’s Human Genetics Commission, and a Fellow of the Academy of Medical Sciences.

The Choosy Reaper: From the Myth of Eternal Youth to the Reality of Unequal Death



Alex Mauron

Professor of Bioethics, Faculty of Medicine,
University of Geneva, Switzerland

Our increased biological understanding of aging has revived prospects for a radical anti-aging medicine and even for the abolition of mortality. Ethicists have often tried to argue against these endeavours, with little success. Arguments appealing to the natural order are either circular or self-defeating. For instance, it is claimed that the death of death would bring evolution to a halt, since no new organisms would come forward to be selected for or against. Now it is true that to have something to work on, evolution “needs” mortality. But who needs evolution? Not *homo sapiens*, who dislikes the prospect of being superseded by a “new and improved” species, unless it has directed its design. Indeed, current post-humanist utopias posit the replacement of blind evolutionary chance by the self-directed reengineering of human nature. Similarly, invoking the invariants of the human condition cuts no ice as rational argument and often turns into an avowedly irrational appeal to the wisdom of the “yuck reaction” evoked by exotic technologies. Does that mean that anti-mortality technologies are ethically innocuous? Not if we consider the reality of unequal death in today’s world. Differences in longevity match the gap between the haves and the have-nots. More interestingly, even in affluent societies where

the basics of food, shelter and medicine are widely available, the Reaper is very much class-conscious (as shown for instance by Marmot's pioneering epidemiological studies). Therefore, until molecular genetics provides new miracles, the best proven recipe for longevity is obvious: be born in a rich country. Even more important: be affluent yourself and/or find yourself in a position of authority. Be the self-reliant, self-satisfied, entrepreneurial type. The life-extending eugenics of tomorrow will increase inequality, not because these technologies are evil in themselves – they are not – but because they will flourish in a world that has turned its back on the passion for equality that was once a hallmark of the Enlightenment.

A Swiss and French citizen, Alex Mauron was born in 1951. Initially trained as a molecular biologist in Lausanne and Stanford, he moved to the field of bioethics during the late eighties. He is presently professor of bioethics at the University of Geneva Faculty of Medicine. He has published widely on the ethical issues of genetics and reproduction, as well as on various issues of medical ethics. He is a member of the Swiss National Advisory Commission on Biomedical Ethics, the Swiss Council of Science and Technology, and the Swiss Academy of Medical Sciences. In addition, he is a regular contributor on bioethics to the Swiss French-language daily *Le Temps*.

Is There Anything Immoral About Wanting to Live Forever?



Arthur Caplan

Professor of Bioethics, University of Pennsylvania, Philadelphia, USA

Most people when asked say they would like to live longer. If not forever, then at least a lot longer than they currently expect to live. Not everyone thinks it is a good idea to live longer lives. Some writers, perhaps, most notably the bioethicist Daniel Callahan argue that the quest to extend life is not a self-evident good. A longer life, Callahan contends, is not necessarily a better life. A nation of much longer lived citizens would wind up unfairly burdening the young. Other writers, such as the philosopher/physician Leon Kass, the political theorist Francis Fukuyama, and the theologian Gilbert Meilander argue that the extension of life should not be pursued because lengthening life is not consistent with human nature. It is “unnatural” to extend human lives beyond the proverbial three score and ten that the demographers assure us is what the average citizen of an economically developed nation can expect. Still scientists are eagerly pursuing research in many species that might lead to life extension in human beings. We do not know enough about aging to know if any of these interventions can deliver a longer life much less immortality. But, should this research be stopped? Are the scientists, physicians and others working on techniques that might lead to significantly longer life spans for human beings engaged, as Callahan, Kass, Fukuyama and others argue, in unethical activities? As this presentation will show, I do not think a persuasive case

against life extension has been made. Indeed, I maintain that research on slowing and even “curing” aging should have greater priority in research budgets than it now does.

Currently, the Emmanuel and Robert Hart Professor of Bioethics, Chair of the Department of Medical Ethics and the Director of the Center for Bioethics at the University of Pennsylvania in Philadelphia. Prior to coming to Penn in 1994, Caplan taught at the University of Minnesota, the University of Pittsburgh, and Columbia University. He was the Associate Director of the Hastings Center from 1984-1987. Born in Boston, Caplan did his undergraduate work at Brandeis University, and did his graduate work at Columbia University where he received a Ph.D in the history and philosophy of science in 1979. Caplan is the author or editor of twenty-five books and over 500 papers in refereed journals of medicine, science, philosophy, bioethics and health policy. He writes a regular column on bioethics for MSNBC.com. He is a frequent guest and commentator in various media outlets. He has served on a number of national and international committees including as the Chair of the Advisory Committee to the United Nations on Human Cloning, the Chair of the Advisory Committee to the Department of Health and Human Services on Blood Safety and Availability, a member of the Presidential Advisory Committee on Gulf War Illnesses, the special advisory committee to the International Olympic Committee on genetics and gene therapy, the American Chemistry Council and the special advisory panel to the National Institutes of Mental Health on human experimentation on vulnerable subjects. He is a member of Dupont’s biotechnology advisory panel, and the board of directors of the Keystone Center and has consulted with many corporations and consumer organizations.

A Futurology of Science and Religion: Immortality Reimagined



Debbona Battaglia

Professor of Anthropology, Mount Holyoke College, Massachusetts, USA

How do alternative science religious communities imagine human life after Apocalypse? What can we learn from their sometimes dangerous, sometimes enlightening visions? And how does mainstream science and bioethical debate figure in the futurology of such religions? Focusing on the Raelian Movement and its neo-Creationist faith in human reproductive cloning, this paper opens a window onto the discursive universe and social consequences of taking Science as God. Specifically, it calls for critical engagement of technoscience spirituality – defined as the effect of “hard faith” in social networking potential of new reproductive technologies – for examining an “ethics of self” in modernity. It also calls for recognition of the media as integral to technoscientific imaginaries, and considers how mediatization shapes, and is shaped by, public culture. In this light, social personhood appears as a project of situated creativity, and of hoping against hope in an age of insecurity. Finally, the paper argues that the ethnography of technoscience “faith-sites,” taken as a valuable supplement to existing disciplinary knowledge of the faith-science relationship might, on the one hand, productively destabilize prior knowledge, and on the other hand, offer a model of and for more densely articulated interdisciplinary engagement.

Debbora Battaglia is the author of *On the Bones of the Serpent: Person, Memory, and Mortality in Sabarl Island Society* (University of Chicago Press) and the editor of *Rhetorics of Self-Making* (University of California Press), and *E.T. Culture: Anthropology in Outerspaces* (in press, Duke University Press). She is currently working on *Galaxies of Discourse: Toward an Anthropological Model of Visits*. Professor Battaglia has also published numerous scholarly articles, including, most recently, "Multiplicities: An Anthropologist's Thoughts on Replicants and Clones in Popular Films," in the journal *Critical Inquiry*, and "Toward an Ethics of the Open Subject: Writing Culture 'In Good Conscience'," in Henrietta Moore, ed. *Anthropological Theory Today* (Cambridge: Polity Press). Professor Battaglia, who received her doctorate from Cambridge University in the field of social anthropology, teaches courses in cultural identities and differences, discourses of the sacred, visualizing culture, peoples of the South Pacific, and introductory anthropology. She has conducted anthropological fieldwork in the islands off the New Guinea coast and urban fieldwork in Port Moresby, Papua New Guinea. She has also worked in Quebec Province, the East Coast of the U.S., and on the Internet with a new religious movement, focusing on faith in science as religion. Her honors include the John Simon Guggenheim Memorial Foundation Fellowship and the National Endowment for the Humanities Fellowship. A frequent presenter and keynote speaker at national and international conferences and academic institutions, she has served as a member of the editorial board of *American Ethnologist*, *Cultural Anthropology*, *Material Culture*, and *Anthropological Quarterly*. She has also served on National Endowment of the Humanities Fellowship panels and on Ph.D. external review committees. In addition to teaching at Mount Holyoke, she has taught courses at the University of East Anglia and Stanford University.



Panel Discussion

Discussion chaired by Geoff Watts
Panelists: Gary Ruvkun, Karin Knorr Cetina
Donald Bruce



Gary Ruvkun

Professor of Genetics, Harvard Medical School,
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Gary Ruvkun is a Professor of Genetics at Harvard Medical School. His lab uses *C. elegans* molecular genetics and genomics to study problems in developmental biology and physiology. Dr. Ruvkun is a graduate of UC Berkeley and Harvard. His PhD thesis with Fred Ausubel explored the symbiotic nitrogen fixation genes of *Rhizobium*. A hallmark of those genes is their conservation over 3 billion years of prokaryotic evolution. Dr. Ruvkun began to work with *C. elegans* as a postdoc with Bob Horvitz at MIT and Walter Gilbert at Harvard, where he explored the genes that control the temporal dimension of development. This work led to the discovery of the first microRNA genes, and the first detection of microRNA genes in other animals, and the discovery of a relationship with RNAi, now an exploding field. Over the past few years, Dr. Ruvkun's lab has discovered that, like mammals, *C. elegans* uses an insulin signaling pathway to control its metabolism and longevity. This analysis has revealed striking congruence of molecular mechanisms at many steps in the pathway, and most importantly, new components also likely to be ancient and universal. These discoveries have implications for treatment of diabetes, a disease of insulin signaling. Using RNAi libraries of nearly every *C. elegans* gene, Dr. Ruvkun's lab has surveyed 17,000 genes for their action in regulation of longevity, fat deposition, and RNAi. This analysis gives a global view of the molecular machines that operate in these pathways. Dr. Ruvkun has also analysed the complete *C. elegans* genome sequence for conserved microRNA and mRNA coding genes. The genome sequence reveals universals in developmental control that are the legacy of metazoan complexity before the Cambrian explosion as well as probable developmental control genes that have been more recently invented or lost in particular phylogenetic lineages. The scientific value of the cartography of these genes is in the power to explain universal features of animal development as well as features that are particular to invertebrates or nematodes.



Karin Knorr Cetina

Professor of Sociology, University of Constance,
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Karin Knorr Cetina is Professor of Sociology at the University of Constance, Germany, Visiting Professor at the University of Chicago, USA, and a member of the Institute for World-Society Studies, University of Bielefeld, Germany. In addition to her three degrees, she has received several honors, including Vienna University's Fellowship for the Gifted. She was a Ford Foundation post-doctoral fellow, a member of the Institute for Advanced Study, Princeton, president of the International Society for Social Studies of Science, and she is a future member of the Center for Advanced Study in the Behavioral Sciences in Palo Alto, CA. She has published numerous papers and books, including *Epistemic Cultures: How the Sciences Make Knowledge* (1999, Harvard), which received the Ludwik Fleck Prize of the Society for Social Studies of Science and the Robert K. Merton Prize of the American Sociological Association. Among other things, she is currently working on information knowledge in global financial markets and preparing a book which analyzes the impact of the life sciences in connection with other developments on social and cultural change in Western societies. The book will have the title *The Culture of Life*.



Donald Bruce

Director of the Society, Religion and Technology Project (SRT) of the Church of Scotland, Edinburgh, UK

Dr. Donald Bruce has been Director of the Society, Religion and Technology Project (SRT) of the Church of Scotland since 1992. He previously spent 15 years in chemistry research in nuclear energy and safety and risk assessment. He holds doctorates in chemistry and theology. The SRT Project was established in 1970 to address ethical and social issues arising from modern technology. For over 10 years SRT has been at the forefront of the ethical debate on a range of biotechnology issues especially GM crops, cloning and stem cells, and has published various seminal books and reports. He has recently spoken on human enhancement issues at debates at the Royal Institution and the Edinburgh International Science Festival and on stem cell ethics at EMBO. He is a member of the public issues advisory committee of the UK Biotechnology Research Council and an observer to the UNESCO International Bioethics Committee. He was a member of the Scottish Science Advisory Committee from 2002-2004. He is a member of bioethics working groups of the Conference of European Churches and the World Council of Churches. He teaches ethics for biotechnology students, is much involved with public engagement and participation on science issues, and is a frequent writer and broadcaster.



2004 winner: Frances R. Balkwill

EMBO Award for Communication in the Life Sciences

Frances R Balkwill is the 2004 winner of the EMBO Award for Communication in the Life Sciences. She receives this honour on account of her excellent work in three principal areas: the writing of an educational book on HIV/AIDS for children in Sub Saharan Africa, which she has developed into a second edition for distribution soon, with the help of a grant from the Bill and Melinda Gates Foundation; the writing of a series of science books for children, and the commissioning and editorial of further similar books; the directorship of the Centre of the Cell project, a new science centre for children, in London.

It would hardly seem that there is time for other work, and yet Professor Balkwill is primarily a practising scientist, and an outstanding one at that. She currently directs the Cancer Research UK's Translational Oncology Laboratory at the Bart's & The London, and is Professor of Cancer Biology at the Bart's & The London, and Queen Mary's School of Medicine & Dentistry at the University of London.

The jury of the EMBO Award for Communication in the Life Sciences commended the winner for her "spectacular work in communicating important scientific concepts and results to the young", and was further impressed by the fact that her efforts extend to communities outside, and less fortunate than, Europe. She was selected from 17 highly rated entries from 9 countries. As winner, she receives a cheque for Euro 5.000, and a hand-crafted medal in silver and gold. EMBO wishes her continued success in science and in communication.

Launched in 2002, the EMBO Award for Communication in the Life Sciences recognises practising scientists in Europe who, as well as being outstanding in

their research, have excelled in communication outside scientific circles. Previous winners are Peter Csermely, Hungary, (2003) and Ronald Plasterk, Netherlands, (2002). The Award makes the winner eligible to be proposed for the European Commission's new Descartes Prize for Science Communication, which places the winners of individual communication prizes in the EU into a larger competition for Europe.

Frances Balkwill's books are available from different publishers, and can be found, for example, via Amazon.

For more information about Frances R. Balkwill see:
<http://www.nesta.org.uk/ourawardees/profiles/1284/>

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acknowledgments

Conference book layout, graphics and editing:
Susanne Späinghaus-Monschau and Halldór Stefánsson

Cover design: Petra Riedinger

Printed by MeraDruck, Sandhausen

Conference organization: EMBL Courses and Conferences Office

Technical support: Trista Dawson, Caroline Hadley, Sarah Sherwood,
EMBL Photolab

Database support: Björn Kindler

Sponsor: Boehringer Ingelheim Stiftung

Credits: Red Hill Studios, Images provided by: J.C. Allen & Son

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The illustrations inside this booklet were borrowed from an animation that was created using a series of eight photographs spanning a woman's lifetime. This set of images shows how she looked at different times in her life. The clip is shown on the web site playingwithtime.org.

