Approches systémiques des différences individuelles de longévité
A systems approach to individual differences in longevity

Institution hosting the chair: Paris Descartes University

Other Academic institution(s) involved in the chair: INSERM

Approches systémiques des différences individuelles de longévité

Si il existe une grande variabilité dans la longévité individuelle, il est très difficile de prédire celle-ci. La variabilité génétique et environnementale joue un rôle clé mais des expériences sur des systèmes modèles en laboratoire montrent que même en éliminant ces effets, on observe toujours des distributions de longévité équivalentes à celles observées par les démographes: un accroissement exponentielle de la probabilité de mourir avec l'âge, suivi par un ralentissement aux âges élevés. **Formation** : en créant une masse critique de scientifiques venant d'horizons disciplinaires complémentaires, la chaire Axa permettra de contribuer à la formation de la première génération de scientifiques qui auront une vision intégrative des différences inter-individuelles en termes de longévité. **Recherche** : ensemble, ces étudiants et ces chercheurs partiront des observations clés faites sur les populations humaines qu'ils chercheront à comprendre en les reproduisant sur des systèmes modèles à temps de génération court. **But** : par une interaction constante entre observations, modélisations et expérimentations sur de larges cohortes où chaque individu sera suivi tout au long de sa vie, ils étudieront les interactions entre phénomènes stochastiques, moléculaires et dynamiques dans le but d'élucider la cinétique du vieillissement et de développer de nouvelles stratégies de prévention ou de traitement.

A systems approach to individual differences in longevity

The long-appreciated high variability of individual longevity is not trivially accounted for. While genetic and environmental differences play a major role, laboratory experiments demonstrated that even in absence of such differences, longevity distributions follow the same pattern as observed by demographers: an exponential increase in death probability with age that decays at old age.
At the *academic level*, the Axa chair will uniquely contribute to form the first generation of high quality researchers having an integrative vision on inter-individual differences in longevity. At the *research level*, the chair will create a critical mass of Axa fellows & researchers of different yet complementary disciplines around a core of European-top researchers together with scientists from the French leading biomedical research faculty of Paris Descartes University. *The aim:* to analyze and reconstruct key observations from human population in well-controlled quantitative large cohort experimental model systems with short generation time where each individual will be followed throughout its lifespan. We will study the stochastic, molecular and dynamic phenomena underlying aging through iteration between observations, mathematical modelling and experiments to elucidate the mechanisms underlying aging kinetics and to develop new prevention or treatment strategies.

Duration of the chair: 60 months

Description

Introduction

The life expectancy of French women has tripled in the past two centuries, gaining approximately one year every four years, thus defying demographers' predictions as demonstrated by Prof. J. Vaupel, one of the future holders of this proposed Chair. Given the decrease in birth rate since the birth of Jeanne Calment (longevity world record, 122 years at death), the ageing part of the population grows rapidly, posing major political, social and economical challenges at the heart of modern societies. While decades' progress in hygiene, medicine and quality of life drastically reduced infant mortality, only modest improvement is felt amongst the eldest. As example, within the French population, the probability to die grows exponential with age, doubling every 8 years, shifting for women (the more robust) from 1:10000 at the age of 10 to 1:10 at the age of 90 . The causes underlying this exponential growth of mortality probability within a year is completely unknown to this date. This pattern was observed already in 1827 by Gompertz, an actuary, who calculated premiums of life insurances. Surprisingly, the mortality curve growth rate remains unchanged ever since we have trustable data: the known progress in life expectancy can be explained solely by a reduction of premature death and decrease of initial mortality and not by slowing of the aging kinetics.

Why some die at the age of ten while others at 122?

Differences in life style or in genetic susceptibilities explain only in part the differences in age of death. Genetic and epidemiological studies have shed light on many risk factors (*e.g.*, obesity, cigarette and alcohol consumption, mutations of oncogenes of repair-related genes). It is however far from trivial to imagine why and how the combination of these factors result in an *exponential* growth of the probability to die at the population level. In order to better understand the relative part of the environmental and genetic factors, animal models were developed. Interestingly, it was shown for instance that one could triple life expectancy of nematodes by changing either their environment or their genes. Astonishingly, even under constant genetic and environmental conditions their mortality curve increases exponentially. This underlies *the importance of stochastic and dynamic phenomena* in potentially explaining the observed acceleration of mortality with age. Such aging patterns were observed in practically all species whereby only the parameters governing the rate change across species, regardless whether unicellular or multicellular organisms are concerned. It thus seems that an internal 'biological clock' exists to govern aging rate in a species-specific manner.

A plead for an interdisciplinary approach to aging: research & education.

While numerous biologists and medical doctors aim at understanding the mechanisms underlying the pathologies whose frequencies increase with age, much rarer are the scientists that work on the understanding of the global mechanisms of this internal clock. To this end, the researchers grouped in this proposed Chair, mathematicians, physicists, engineers, chemists, geneticists, evolution and motricity specialists, demographers, psychologists and epidemiologists, have the needed collective capacity to tackle this challenge through a quantitative, comparative and truly interdisciplinary integrative approach. By applying Systems approaches, we will combine observations from humans (WP1), experiments on model systems as mice, flies, worms (WP2), yeast and bacteria (WP3) together with mathematical modelling to produce data that will enable to propose and test different hypothesis that may explain from the molecular dynamics level, the observed exponential increase in death probability and its late-age digression. By following systematically, for humans as for our experimental models, sufficiently large numbers of individual trajectories and by modelling and statistically analysing these trajectories and their variability, we will attempt to understand why some die before others. By observing the correlations between the probability of dying and molecular or behavioural characteristics, we would be able to test their causalities and different intervention modalities. Surpassing disciplinary borders, the Axa Chair collaborators will form, through dedicated fellowships, courses & seminars, conferences and workshops, the 1st generation of scientists to address in an integrative manner these core questions underlying aging that are easier to pronounce than to define and tackle. Is aging the result of aging of particular components (in this case, which?) or an emerging property of a complex system? We will try to understand why, in humans as in nematodes, a mortality decrease appears at advanced old age and what are the mechanisms ruling this slowing down of the internal clock. Though opting for a fundamental research approach our research is both applied and may be extended to the clinic. The resolution of the questions we wish to address will most certainly have a strong impact on human health and well-being by elaborating new prevention strategies as well as potential targets for treatment and medication.

Proposed Research *(Coordinator: F. Taddei)*

The proposed Axa Chair will support interdisciplinary research axed around three main Work Plans, maximising the interaction and inter-group fertilisation between the chair holders and Paris Descartes researchers. The chair aims at integrating the efforts of top notch international groups across the different aging time scales and species. Each WP will be reinforced by Axa Chair postdoctoral fellows; the hosting labs will provide the appropriate funding and infrastructure for the projects.

WP1: Towards better understanding of individual differences in mortality in humans

Associated Chair holders: T. Kirkwood, J. Vaupel
Associated researchers: E. Riboli, M.-A. Ergis, F. Taddei, J.-C. Thalabard, P.-P. Vidal

Using advanced demographical analysis, we will address longevity variability among and within countries over time and analyse correlations with factors such as GNP, medical expenditures, socio-economic level or literacy. Interestingly, the latter two are amongst the best predictors of life expectancy[3]. We will focus on their effect on the whole mortality distribution. This analysis will be complemented by epidemiological case-controlled studies as the most potent approach to analyse factors like diet, education, mobility and environment on carefully documented clinical progress of life-threatening diseases with age.

WP2: Quantitative animal model experimental systems

Associated Chair holders: T. Kirkwood, L. Partridge
Associated researchers: I. Matic, F. Taddei, P.-P. Vidal

We will focus on following individuals of the best studied animal models (mice, flies and worms) throughout their life span and manipulate their environment, diet or motricity to test further the correlations observed in human studies (WP1). As examples, (i) experiments will provide insight to the role of diet and bacterial flora on aging, following observations that link the latter in our animal models with changes of parameters of the above-decribed death probability patterns. (ii) In humans, mice as in nematodes a decrease in motricity is associated with elevated probability of dying. We will take advantage of the latter simple, well-defined experimental systems to study treatment modalities that stimulate motricity and quantify their influence on aging. (iii) We will further study the genetic and environmental parameters susceptible to change death probability parameters and to increase life span, extending upon the state of the art results of Prof. L. Partridge, a future holder of the proposed Chair, that demonstrated that caloric restriction, even when initiated at old age, could decrease mortality[4].

WP3: Aging in unicellular organisms: dissection of underlying dynamics of molecular phenomena

Associated Chair holders: J. Vaupel
Associated researchers: A. Lindner, L. Moisan, I. Svetec, F. Taddei

Bacteria has recently joined yeast as a unicellular model for aging[5], linking aging to hazard and degeneracy in bacteria and implying the role of protein aggregation (linked to many age-related human diseases) to bacterial aging[6]. These results open the door to the understanding of the importance of stochastic and dynamic molecular aspects of aging[7]. This WP will aim at extending our knowledge on the dynamic interplay between molecular factors, changes in physiology, epigenetic inheritance and longevity as we can quantify the life history of each bacteria and yeast individual within their lineage context through state of the art live microscopy, tailored image analysis and statistical tools while monitoring protein expression and accumulation of molecular damages in different genetic backgrounds. Furthermore, our advanced nanofabrication and micro-fluidics expertise will enable us to alter dynamically the environment at will and thus test the stressful or hormetic impact of environmental perturbations, decipher the molecular pathways involved in maintenance and degeneracy as well as the influence of different diet regimes.

Academic activities : The Axa Ageing program

During the 5 years of the proposed chair, 25 top students will be selected for international Junior Chair Fellowships to support their Master's rotations in labs that will include a Chair holder and at least one Paris Descartes research group. This will maximise the number of students that will be exposed to interdisciplinary aging research as well as the impact of the Chair and the collaboration between groups. *Individualised Training of international Axa aging Fellows* Each Axa Chair student and postdoc will be invited to follow an individualised training in the courses offered by Paris Descartes and its partners. A typical fellow would have a solid disciplinary background (medical, social or natural sciences) and a clear motivation to develop quantitative analysis of aging. The international fellows will be offered simultaneously french courses and tailored interdisciplinary programs in english in Paris Descartes university or its partners. As acquiring a broad education on aging and quantitative tools require time, the Axa aging junior fellows will be invited to join as first or second year of master depending on their past experience. They will select both quantitative courses and aging courses during their master and will be doing rotations in different partner labs (in Paris or abroad) to acquire the complementary tools characteristics of different disciplines. After their master, they will be invited to perform interdisciplinary PhD with cosupervision in 2 of the labs involved in the program. The tailored program will include seminars from the Chair holders and associate researchers, the Axa Aging discussion club (at the University's Center for Research and Interdisciplinarity - CRI, www.cri-paris.fr), 3 international conferences and a bi-annual summer school. All these activities will be open (limited by space) to the participation of local and international students and scientists to maximise the visibility and effectivity of the Chair.

Chair organisation

Governing ('Orientation & Evaluation') and scientific coordination (' steering') committees will be set (as described in the Convention draft in annex) to assure the optimal functioning of the Chair, prioritise its activities and select the junior and postdoctoral fellows.

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[3] Riley, Rising life expectancy, a global history 2001; [4] Stewart, PLoS Biol. 2005; [5] Mair, Science, 2003; [6] Lindner, PNAS, 2008; [7] Kirkwood, Mech. Aging & Dev 2005

Chair holders

The proposed Chair holders were selected amongst the top world researchers in the field of ageing, for their mastering of complementary, yet non-overlapping fields as well as for their excellent teaching record.

Prof. Thomas Burton Loram KIRKWOOD (www.ncl.ac.uk/iah/staff/profile/tom.kirkwood)
PhD, University of Cambridge, UK (Biology). Professor of Medicine, Newcastle University, United Kingdom. Director of the Institute for Ageing and Health and of the Centre for Integrated Systems Biology of Ageing and Nutrition. Member of the editorial boards of PLoS Biology, Age & Ageing, Theoretical Biology journals. 291 scientific publications (177 peer-review papers) and 5 books. *Research interests:* Molecular genetics of ageing and longevity; molecular and cellular biology of ageing; age-related diseases; comparative and evolutionary biology; biomathematical modelling of cell and molecular processes.

Prof. Linda Partridge (www.ucl.ac.uk/~ucbtcee/flies/Linda_Partridge.html)
PhD, University of Oxford, UK (Zoology). Weldon Professor of Biometry and Director of the UCL Institute of Healthy Ageing, Centre for Research on Ageing, Department of Genetics, Evolution and Environment, University College London, United Kingdom. Fellow of the Royal Society and of the Academy of Medical Sciences, EMBO member, awardee of 'Living Legend, Help the Aged'. *Research interests:*). Functional genomic analysis of ageing, Role of MicroRNAs in phenotypic plasticity to environmental change, Role of nuclear hormone receptors in determination of lifespan in *Drosophila,* response of lifespan and fecundity to dietary restriction, Evolutionary genetics of human nutrition, signalling in the ageing brain: improving fruit-fly models, translating to human studies.

Prof. James W. Vaupel (www.demogr.mpg.de/)
PhD, Harvard, Boston, USA (Mathematical statistics and Public Policy). Founding and Executive Director of the Max Planck Institute for Demographic Research, Head of the Max Planck Laboratory of Survival and Longevity and the Laboratory of Evolutionary Biodemography, Rostock , Germany. Scientific Member of the Max Planck Society for the Advancement of Science, Regular Scientific Member of the U.S. National Academy of Sciences, Fellow of the American Academy of Arts and Sciences. Over 200 publications. *Current research interests include:* Age-trajectories of Growth and Their Implications for the Evolution of Mortality, Comparative Studies of Sex-specific Mortality Trajectories, Lifespan Disparities at Younger Ages, Reconstructing Age-specific Mortality Profiles in Ancient Human Populations, Unifying Models of Life´s Trajectories.

Dr. François Taddei (www.necker.fr/tamara)
First trained in mathematics and physics and then followed the interdisciplinary curriculum of the French Ecole Polytechnique. He received an engineering master (ENGREF) as well as master and PhD degrees in Genetics (Paris XI University). His scientific work was recognized by awards from INSERM, Bettencourt foundation, EURYI and HFSP for its interdisciplinary approaches to bacterial aging, genetic and phenotypic variability, its molecular causes and its medical and evolutionary consequences. He currently leads an INSERM team in Paris and serves as the director of the Center for Research and Interdisciplinarity, the Frontiers in Life Sciences European Interdisciplinary PhD program and of the Interdisciplinary Approaches to Life Sciences Master Program. Regular reviwer of leading journals (Nature, Science...). Member of France 2025 a gouvernemental think-tank aiming at preparing scenario for national future.

Chair associate researchers

Dr. Annette Baudisch (http://www.demogr.mpg.de/en/staff/baudisch/)
Deputy director of MaxNetAging research school and a research scientist at Max Planck Institute for Demographic Research, Rostock, Germany. Reviewer for *Theoretical Population Biology*, *Evolution*, *Demography* and *Demographic Research* journals. Recipient of Max Planck Society's highest award for excellence in doctoral research (Otto Hahn Medal). Educated in both mathematics and biology, her scientific interests are modeling biodemography of aging and evolutionary demography.

Prof. Anne-Marie Ergis (http://ed261.psycho.univ-paris5.fr/spip.php?article45)
Professor of psychology (neuropsychology of aging) at University Paris 5. Associate researcher at Centre de Recherche de l'Institut Universitaire Geriatrique de Montreal, Montreal, Canada. Responsible of Master SHS Mention Psychologie, Specialite "Psychologie Gerontologique" at Institute of Psychology, University Paris 5. Member of French psychology societies (SNLF, l'AEPU, FFPP, CPCN, GRECO, SGGIF...) With 30 articles published in peer-reviewed journals and more than 25 book chapters, her research interest include memory changes in Alzheimer's disease and depression in elderly.

Dr. Ariel Lindner (www.necker.fr/tamara)
INSERM Junior Researcher at INSERM U571, University Paris 5, Paris, France. Co-coordinator of French Synthetic Biology Research Network. Director of studies and co-founder of Centre for Research and Interdisciplinarity (CRI), University Paris 5. Former Marie Curie, EMBO and FEBS fellow. Trained as a chemist, and educated in genetics, he is interested in cellular aging in microorganisms, image analysis and single-cell microscopy.

Prof. Lionel Moisan (http://www.math-info.univ-paris5.fr/~moisan/)
Professor of mathematics at University Paris 5, Paris, France. Former CNRS researcher at Ecole Normale Superieure de Cachan. His research interests are mathematical modelling of human and artificial vision, detection of structures in images, image restoration using variational methods and subpixel image processing.

Dr. Ivan Matic (www.necker.fr/tamara)
Research director (CNRS), INSERM U571, University Paris 5, Paris, France. Reviewer for *Biochemistry*, *Cell*, *DNA Repair*, *EMBO Journal*, *Gene*, *Genetics*, *Journal of Microbiology*, *PNAS*, *PloS*, *Science* etc. Associated Editor of *PloS Genetics*. Recipient of award "Pour les Sciences du Vivant", Liliane Bettencourt-Schueller Fondation. His scientific interests range from SOS and mismatch repair mechanisms, stress-induced mutagenesis to host-pathogen interactions and aging in bacteria and nematodes.

Prof. Elio Riboli (http://www1.imperial.ac.uk/medicine/people/e.riboli/)
Professor of cancer epidemiology and prevention and head of the Division for Epidemiology, Public Health and Primary Care at the Faculty of Medicine, Imperial College London, London, UK. Head of the Unit of Nutrition, Hormone and Cancer with the EPIC (European Prospective Investigation into Cancer and Chronic Disease). Member of editorial board of *European Journal for Clinical Nutrition*, *Public Health Nutrition* and *Cancer Epidemiology, Biomarkers and Prevention*. Reviewer for *Nature Cancer Review*, *Nature Genetics*, *International Journal of Epidemiology*, *British Journal of Cancer* etc. Member of numerous associations in France, Italy and USA. As a medical doctor with a master degree in epidemiology, his interests are cancer associated genetic variability in humans and life style influence on cancer incidence.

Dr. Ivan-Kresimir Svetec (http://www.pbf.hr/hr/zavodi/zavod_za_biokemijsko_inzenjerstvo/laboratorij_za_biologiju_i_genetiku_mikroorganizama/ivan_kresimir_svetec)
Assistant professor at Faculty of Food Technology and Biotechnology, University of Zagreb, Zagreb, Croatia. Co-leader of the joint project "Genetics of death in yeast" at the Mediterranean Institute for Life Sciences, Split, Croatia and INSERM U571, University Paris 5, Paris, France. With a strong background in biotechnology, cellular biology and genetics, his research include gene targeting, palindrome content in yeast genome, evolution of sex and genetics of aging and death.

Prof. Jean-Christophe Thalabard (http://www.math-info.univ-paris5.fr/~thalabard/index.html)
Professor of biostatistics at University Paris 5, Paris, France. Senior consultant in Reproductive Medicine, Unit of Endocrinology and Reproductive Medicine, Hotel-Dieu, AP-HP, Paris. Member of UMR CNRS 8145 MAP5, University Paris 5. Co-organizer of Master degree in biostatistics, University Yaounde 1, Cameroon. Member of International Society for Clinical Biostatistics, French Society of Senologia, French Society of Endocrinology and ADELF. With both medicine and biostatistics doctorates held, he is interested in methodology of clinical trials and regulation of human fertility.

Prof. Pierre-Paul Vidal (http://www.biomedicale.univ-paris5.fr/lnrs/fr/fiches/ppv.html)
Founder and head of CNRS UMR 7060, University Paris 5. Vice-president of scientific council of UFR Biomedicale des Saints Peres at University Paris 5. Member of National Council for Medical Studies. Member of editorial board of *Experimental Brain Research* and *Vestibular Research*. Organizer of numerous symposia on neurobiology of sensory motors. More than a 100 peer-reviewed publications and 30 book chapters. His scientific research focuses on *in vivo* and *in vitro* approaches to study models of behavior, such as gaze and postural control, and novel treatments of neurological disorders.

Additional invited researchers

Dr. Pascal Hersen (http://www.msc.univ-paris7.fr/~phersen/Hersen_home.html)
CNRS research scientist at Complex matter and systems laboratory, University Paris 7, Paris, France. Member of the AIV Master Program administrative board. Reviewer for *Physical Review Letters*, *Geophysical Research Letter* and *Physical Review*. With his background in physics and systems biology, his scientific interests include a variety of topics, from morphology of sand dunes to locomotion activity in nematodes.

Dr. Hong Qin (http://qinresearch.net/ and http://bioinformatics.org/ctls/)
Assistant professor at Tuskegee University, Alabama, USA. Researcher in computational biology and bioinformatics. Developer of computational biology curriculum for undergrad and master level, Tuskegee University. With his knowledge in computer science, biophysics, biochemistry and molecular biology, his research interests include statistical genetics and genomics, computational biology and modeling of aging and natural variation.