

Translational Antiaging Research

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Introduction

APPROXIMATELY 200 WORLDWIDE RESEARCHERS attended the fourth SENS Foundation's conference at Queens' College in Cambridge, UK, September 3rd–7th, 2009. SENS conferences are distinguished from other biogerontological and aging research conferences by having more of an applied focus on antiaging therapies. The main subfields of aging research covered at SENS4 were intracellular and extracellular junk buildups, telomeres and cancer, immunology, therapeutic delivery, stem cells, and tissue engineering. Key findings included eliminating accumulated waste through small molecule binding, *de novo* enzyme design, genetic recombination using zinc finger proteins, and intranasal stem cell delivery to the brain.

Broad Conference Themes

The strongest overall theme that continues to shape the current scientific understanding of aging is the complexity and systemic nature of the phenomena. Mechanisms for reversing aging that work in lower organisms (e.g., yeast, plants, worms, flies), such as any one of 200 knockout genes or caloric restriction in mice, may not work or definitely will not work in the more complex regulatory systems of higher mammals such as humans. Researchers are holding multiple possibilities in mind simultaneously, such as the idea that inflammation and plaques are to be eliminated versus the idea that plaques are the body's protective response to the real underlying disease trigger. Multidisciplinarity continues to be a theme, integrating both life sciences fields and life sciences with technology fields such as imaging and computational modeling. A third theme is a dual focus on both physical state and cognitive function as being equally important in aging. A fourth theme is the start of genomic data's use in evaluating aging pathologies.

Highlight Talks

There were many interesting lectures, a few of which stand out as being exceptional in extending the contemporary progress of antiaging research in the areas of eliminating accumulated waste, reprogramming aging processes, and stem cell research.

Eliminating accumulated waste

One of the key areas in antiaging therapies is eliminating the variety of intracellular and extracellular waste that builds

up with age-related diseases such as macular degeneration, atherosclerosis, and Alzheimer's disease. The SENS Foundation sponsors ongoing work in this area, and two talks highlighted recent progress. First, in the area of eliminating amyloid was Mark Pepys (University College London, London, UK) discussing the "Treatment and Prevention of Amyloidosis."¹ The methodology employed is to take advantage of the body's natural mechanism of clearing away foreign plasma proteins by binding small molecules (e.g., the new molecule CPHPC) to uncleared waste (e.g., harmful serum amyloid P [SAP]) to form a new protein for automatic disposal. The same method is being investigated to cross-link and expel other molecules such as transthyretin. Second, in the area of rejuvenating extracellular material, Kendall Houk (UCLA, Los Angeles, CA) presented "Designing Enzymes *Ab Initio*."² This method uses computational physics and chemistry for *de novo* enzyme design by looking for theozymes, theoretical enzymes with the requisite binding sites and other properties via computational search and molecular dynamical simulation. A portfolio of new proteins and enzymes has been synthesized and tested, for example retroaldolases and Diels-Alderase, which might be able to remove the advanced glycation end products (AGEs) of aging.

Reprogramming aging processes

A second critical area for antiaging therapies is to be able to reverse, manage, or reprogram the processes that occur with aging. First, landmark research in the area of genetic recombination was presented by Carlos Barbas (Scripps, La Jolla, CA) "Synthesis of Programmable Integrases."³ This technique provides a more specific alternative to the homologous recombination method of genome modification by using zinc finger proteins to reprogram serine recombinases. A second talk indicating recent progress concerned combating oxidation, with Vladimir Skulachev (Moscow State University, Moscow, Russia) presenting "Mitochondria-Targeted Plastoquinone Derivatives as Anti-Senescence Drugs."⁴ This method uses a hydrophobic cation, SkQ1 (a structural analog of plastoquinone), to reduce mitochondrial reactive oxygen species (ROS). The SkQ1 molecule will be entering clinical trials in the fall of 2009 with a Russian pharmaceutical company for the treatment of glaucoma.

Stem cell research

A third important area in antiaging is stem cell research as a means of rejuvenation therapies. A particular talk of note in

this area concerned stem cell delivery as Lusine Danielyan (University of Tübingen, Tübingen, Germany) discussed “Intranasal Delivery of Cells to the Brain.”⁵ This method uses intranasal delivery of mesenchymal stem cells (MSCs) and glioma cells for the rapid (within 15 min) routing of neurotherapeutics deep into the frontal cortex and striatum of mice. Second, looking at novel routes to the embryonic stem cell-like state was a talk by Justin Ichida (Harvard University, Cambridge, MA) “Reprogramming Somatic Cells to Pluripotency Using Small Molecules.”⁶ This method uses a functional reprogramming screen to identify small molecules to replace signaling factors as fibroblasts are taken back to induced pluripotent stem cells (iPS), avoiding the oncogenesis that can occur with current techniques.

Most Contentious Talks: Stem Cell Retrodifferentiation and Oocyte Rejuvenation

The two talks the attendees found most contentious were “Retrodifferentiation and Aging: Harnessing Youth through Induction of Pluripotency in Mature Adult Cells via Cell Surface Receptor Contact,” presented by Ilham Abuljadayel (TriStem, London, UK), which discussed the retrodifferentiation of white blood cells using multiclonal antibodies into other cell types such as red blood cells, neurons, and heart cells,⁷ and “Progress Toward Use of Adult Ovary-derived Stem Cells as Therapeutic Tools and Targets for Delaying Age-related Infertility and Menopause,” presented by Kaisa Selesniemi (Massachusetts General Hospital and Harvard Medical School, Boston, MA), which discussed the possibility of using stem cell-based regenerative medicine to sustain ovarian function (fertility) in aging females.⁸

ELSI and Technological Adjacencies: Zoomers and Diamond Mechanosynthesis

Because aging research is an emerging and wide-ranging field, ethical, legal, and social issues (ELSI) and related technological adjacencies were covered at SENS4. The most interesting ELSI talks featured an empowering rebranding of seniors as “Zoomers” in a keynote and video by Moses Znaimer, CEO of Toronto-based ZoomerMedia,⁹ and one of the first looks at the “Demographic Consequences of Defeating Aging” by Leonid Gavrilov (University of Chicago, Chicago, IL).¹⁰

Important technological adjacencies presented included a talk by Adela Ben-Yakar (University of Texas, Austin, TX) “Femtosecond Laser Nanosurgery from Shedding Light on Nerve Regeneration to Aiding in Cancer Diagnosis and Therapy.”¹¹ This technique discussed the use of *in vivo* femtosecond laser nanoaxotomy on a chip with single-cell ablation capability for cancer treatment and other targeted therapeutics. Gunther Kletetschka (GSFC/NASA, Greenbelt, MD) presented another interesting talk, “Crack Avoidance during Cryopreservation Attempts” by using a magnetic field (the magnetocaloric effect) for uniform cooling.¹² A third important talk with an eye to the longer term was presented by Philip Moriarty (University of Nottingham, Nottingham, UK), “Molecular Nanotechnology in the Real World: How Feasible is a Nanofactory?,” looking at the possibility of diamond mechanosynthesis reactions and their use in nanomedicine.¹³

Immediately Actionable Research

Encouragingly, three research ideas for immediate implementation were discussed at SENS4. First was a nutritional study regarding the consumption of blueberries, raspberries, strawberries (any berries, 4–8 oz per day), walnuts (1 oz per day), and green tea (1 cup per day) to decrease the mental aspects of aging and maintain a healthy polyunsaturated fatty acids (PUFA) ratio. (“Quenching the ‘Fires’ of Inflammatory and Oxidative Stress: Implications for Healthy Brain Aging” by James Joseph [Tufts University, Boston, MA]).¹⁴

A second practicable example was a study that found that French herbs, particularly savory, marjoram leaves, rosemary leaves, basil, sage, and tarragon, when consumed as a tea or in capsule form (2×350-mg savory capsule) provided an aging-related cell surface nicotinamide adenine dinucleotide (NADH) oxidase (arNOX) reduction from 40% to 15% for 6–9 h following consumption. ArNOX oxidizes (renders unhealthy) low-density lipoprotein cholesterol (LDL-C). (“Aging Related NADH Oxidase [arNOX] Response to Dietary Supplementation: The French Paradox Revisited” by D. James Morré [Purdue University, West Lafayette, IN]).¹⁵

Third, regarding exercise, was the suggestion of an IHT (intermittent hypoxic [low oxygen air] training) regimen of 5 min of exercise, 5 min of pausing intervals using a hypoxicator to simulate altitude training (“Affordable Rejuvenation: A Prototype Facility in Action” by Arkadi Prokopov [Son Baulo Medical Spa, Mallorca, Balears, Spain]).¹⁶

Venture Capital Guide to Antiaging Biotechnology Investing

Several promising startup companies focused on the nascent but significant and growing antiaging biotechnology space were present or discussed, as they are making progress in translational antiaging therapies:

1. Epeius Biotechnologies, San Marino, CA: Rexin-G, a tumor-targeted injectable gene delivery system
2. FoldRx, Cambridge, MA: Small molecule therapeutics to treat protein misfolding diseases, and bind and clear undesired molecules
3. Gencia Corporation, Charlottesville, VA: Mitochondrial DNA rejuvenation using the rhTFAM (recombinant-human mitochondrial transcription factor A) protein
4. Genescent, Fountain Valley, CA: Novel chronic disease therapeutics by combining genomics and selective screening (a large Alzheimer’s disease genetic study is in progress with Kronos and TGen)
5. Knome, Cambridge, MA: Whole human genome sequencing (consumer offering)
6. Neotropix, Malvern, PA: Oncolytic viruses for the treatment of solid tumors
7. Pentraxin Therapeutics Ltd, London, UK: Small molecule drug CPHPC specifically targeting SAP (serum form of amyloid P) and removing it from the blood and brains of Alzheimer’s disease patients
8. Repeat Diagnostics, Vancouver, BC, Canada: Telomere length measurement for total lymphocyte and granulocyte populations (consumer offering)
9. Retrotope, Los Altos Hills, CA: Using isotope effect to slow down damage pathways and control metabolic processes associated with oxidative stress

10. StemCor Systems, Inc., Menlo Park, CA: Bone marrow harvesting system
11. T.A. Sciences, New York, NY: Telomerase activation via the single molecule TA-65, licensed from Geron Corporation (consumer offering)
12. TriStem Corporation, London, UK: Retrodifferentiation technology to create stem cells from mature adult cells.

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