The Tasks of Longevity Promotion:

Science, Ethics and Public Policy

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http://www.longevityhistory.com/

http://www.longevityforall.org/

http://isoad.org/



Healthy Life Extension – How? Why? Who?

- 1. Feasibility
- 2. Desirability
- 3. Action



<u>1. Feasibility</u> Aging – the Main Risk Factor of Non-Communicable Diseases



http://web.stanford.edu/group/brunet/background.html



right rearrouts unseases and aging time industries or major torionic diseases rises explorentially with age, as shown: cardiovascular disease (blue squares) (data from (22)), cancer (red diamonds) [data from (22)], AD (gray squares) (data from (23)] and influenza-associated hospitalization (green triangles) (data from (24)). Incidence rates enormalized to the stociated hospitalization (green triangles) (data from (24)). Incidence and a normalized to the stociated hospitalization (green triangles) (data from (24)). Incidence rates enormalized to the stociated hospitalization (green triangles) (data from (24)). Incidence rates enormalized to the stociated hospitalization (green triangles) (data from (24)). Incidence rates enormalized to the stociated hospitalization (green triangles) (data from (24)). Incidence rates enormalized to the stociated hospitalization (green triangles) (data from (24)). Incidence rates enormalized to the stociated hospitalization (green triangles) (data from (24)). Incidence rates enormalized to the stociated hospitalization (green triangles) (data from (24)). Incidence rates enormalized to the stociated hospitalization (green triangles) (data from (24)). Incidence rates enormalized to the stociated hospitalization (green triangles) (data from (24)). Incidence rates enormalized to the stociated hospitalization (green triangles) (data from (24)). Incidence rates enormalized to the stociated hospitalization (green triangles) (data from (24)). Incidence rates enormalized to the stociated hospitalization (green triangles) (data from (24)). Incidence rates enormalized to the stociated hospitalization (green triangles) (data from (24)). Incidence rates enormalized to the stociated hospitalization (green triangles) (data from (24)). Incidence rates enormalized to the stociated hospitalization (green triangles) (data from (24)). Incidence rates enormalized to the stociated hospitalization (green triangles) (data from (24)). Incidence rates enormalized to the stociated hospitalization (green tri

www.ScienceTranslational Medicine.org 14 July 2010 Vol 21ssue 40 40cm21 1

The Demographic and Biomedical Case for Late-Life Interventions in Aging

Michael J. Rae,1 Robert N. Butler,2* Judith Campisi,3 Aubrey D. N. J. de Grey,1 Caleb E. Finch,4 Michael Gough,5 George M. Martin,6 Jan Vijg,7 Kevin M. Perrott,8 Barbara J. Logan8††. *Science Translational Medicine.* Published 14 July 2010; Volume 2 Issue 40 40cm21

http://stm.sciencemag.org/content/2/40/40cm21.full

Aging is not commonly considered a risk factor for disease



www.thelancet.com Vol 380 December 15/22/29, 2012

Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. (2012). A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010, Lancet, 380:2224-2260.

But it should be!

2245

To extend healthy life – we need to ameliorate degenerative aging!

If the Degenerative Aging Processes are the Main Risk Factors for Diseases – The aging processes should be addressed preferentially! Can we postpone, or even reverse those processes? Yes. We Can!

| Basic Aging Process | Disease | Potential Treatment |
|----------------------------------|---------------------------------------|--|
| Inflammation ("Inflammaging") | Heart Disease, Cancer | Immune-modulating substances |
| Cross-linkage | Atherosclerosis | Enzymatic hydrolysis, Oxido-reductive depolimerization, immunoclearance |
| Demineralization | Osteoporosis | Supplementation |
| Loss of DNA Repair | Cancer | DNA Repair Enhancement |
| Stem cell depletion | Neurodegenerative diseases | Stem cell therapy |
| Beta Cell senescence | Diabetes | Cell therapy, elimination of senescent cells |
| Naïve T cell depletion | Susceptibility to infectious diseases | Thymus regeneration |

Can we extend Healthy Longevity? Yes, we can! <u>Feasibility: Some sources of hope</u>

Life expectancy increases

Life expectancy 1950-2005



Technology advances



Long-lived/non-aging Life-forms



Experimental life-extension



The Pursuit of Longevity is ancient But its **scientific pursuit** is young Just about 100 years old

Elie Metchnikoff (1845 – 1916)



Charles-Édouard Brown-Séquard (1817 – 1894)



New Therapies were developed in the study of aging and longevity

Cytotoxic Serum (Immunotherapy), Probiotic Diet – 1900s

Hormone Replacement Therapy - 1889

www.longevityhistory.com

http://online.liebertpub.com/doi/abs/10.1089/rej.2013.1527

Some un-orthodox methods were proposed for the combat of aging and extending longevity (1900s-1930s) Though flawed – they were important for the development of medical technology

Subtraction - resections:

- Colectomy (William Arbuthnot-Lane, 1856 – 1943)
- Appendectomy
- Tonsillectomy
- Hysterectomy

<u>Addition:</u> Blood transfusion – Alexander Bogdanov (1873-1928)





Section to be removed during surgery

Lane's colectomy

Carrel's Perfusion Pump

Addition - Transplantations:

- Sex Gland Transplantation (Heteroplastic) - Serge Voronoff (1866 – 1951)
- Sex Gland Vasoligation (Autoplastic) - Eugen Steinach (1861 - 1944)
- Culture of Organs Alexis Carrel (1873 – 1944)



Before and After Steinach's Operation

After the war – medical technologies advance dramatically, making elimination of damage and replacement of aging organs feasible (1950s-1970s)

Subtraction – Elimination of Damage

- Antibiotics
- Immunosuppressants
- Chemotherapy
- Antioxidants
- Laparoscopy





Laparoscopic procedure

Hip replacement

Addition – Tissue replacement

- Biological Transplants:
- Artery bypass graft (1953), human kidney (1954), heart valve (1955), bone-marrow containing adult stem cells (1956), liver (1963), lung (1963), hand (1964), pancreas (1966), heart (1967), head (in a monkey, 1963). Cryopreservation (1952, 1967).
- Bionic Transplants and Resuscitation devices:
- Heart valve (1951), cardiac pacemaker (1952), heart and lung machine (1953), artificial kidney – dialysis machine (1955), artificial hip replacements (1962), the first prototypes of biosensors and artificial blood (1962), a computercontrolled arm (1963), synthetic skin (1965), cardiac stent (1964, 1977).

Interventions now reach the genetic level (1990s-2010s) Genetic engineering

Subtraction Gene Inhibition for "Aging Accelerating Genes":

> DAF, mTOR, IGF, NF-κB RNA Interference

Addition

Gene Stimulation for "Longevity Genes":

> Sirtuins, FOXO, Klotho, cholesteryl ester transfer protein (CETP), Telomerase



Gene Inhibition/Stimulation

Gene Splicing

DNA Repair

RNA Interference

There is a need to consider epigenetic – environmental factors in relation to the genes <u>http://www.senescence.info/genetics_of_aging.html</u>

Geroprotectors – Substances

to delay degenerative aging processes and extend healthy longevity



Working through subtraction of damage vs. addition of deficits – Toward Balance

The correct dosage is vital ("The Dose makes the Poison")

Subtraction / Detoxification

- Chelation
- Enterosorbents
- Statins
- Anti-inflammatory
- Anti-glycemic
- Anti-oxidant
- Anti-coagulants



http://www.denigma.de/lifespan/interventions/?manipulation=12

Addition / Supplementation

- Hormone Replacement Therapy
- Hyaluronan
- Vitamins
- Microelements
- Macroergics
- Mitochondrial modulators
- Peptide bio-regulators



http://genomics.senescence.info/drugs/ http://www.geroprotectors.org/ http://ageing-map.org/

The interventions reach the molecular/nano level – Nanomedicine

Subtraction

- Carbon and Gold nano-shells to eliminate cancer and senescent cells
- Targeted Drug Delivery (Liposomes)
- "Artificial immune cells"
- are in Research and Development

Addition

- C60 fullerene nano-particles
- Artificial Cells such as:
- "Nanobots" for molecular repair
- "Artificial respirocytes" for oxygen delivery

are in Research and Development



Gold nano-shells



Artificial Immune Cells



Artificial Respirocytes (Oxygen Delivery)

http://www.understandingnano.com/medicine.html http://www.foresight.org/Nanomedicine/ Strategies for Engineered Negligible Senescence (SENS) "The 7 Deadly Things"

• <u>Subtraction</u>:

- 1) Death-resistant cells to be removed by targeted ablation (ApoptoSENS)
- 2) Tissue stiffening to be prevented by compounds breaking Advanced Glycation End-products – AGE-breakers (GlycoSENS)
- 3) Extracellular aggregates to be cleaned up by immunotherapeutic clearance (AmyloSENS)
- 4) Intracellular aggregates to be dissolved by novel lysosomal hydrolases (LysoSENS)
- 5) Nuclear (epi-)mutations leading to cancer to be neutralized by the removal of telomere-lengthening machinery (OncoSENS)

http://www.sens.org/

https://mfoundation.org/

• Addition:

- 6) Cell loss and tissue atrophy to be replenished by adding stem cells and tissue engineering (RepleniSENS)
- 7) Mutant mitochondria to be backed up by allotopic expression of 13 proteins in the nucleus (MitoSENS);



SENS Foundation advancing rejuvenation biotechnologies

Regenerative Medicine

Subtraction

Cell removal

- Apoptosis regulated cell death
- Tumor Suppression
- Removal of senescent cells



http://en.wikipedia.org/wiki/Tissue_engineering https://en.wikipedia.org/wiki/Regenerative_medicine http://www.wakehealth.edu/WFIRM/

Addition

Cell replenishment

- Induction of regeneration
- Stem cells and their products
- Tissue engineering (bioreactors / scaffolds/ tissue printing)









Robotics/Bionics/AI

Subtraction:

Robotic Surgery



Data mining



http://en.wikipedia.org/wiki/Artificial_organ http://www.humanlongevity.com/

Addition:

- Artificial Limbs
- Artificial Organs
- Exoskeletons
- Brain-Computer Interfaces/Neuro-prosthetics



Artificial Heart



Robotic Arm



Brain-Computer Interface Neuro-prosthetics



Exoskeleton

Holistic Treatments for Extending Longevity

Moderation - Rest - Meditation



Natural Nutrition



Exercise



Electromagnetic Therapy



2. Desirability

Life Extension – Expression of the Valuation of Life



HERBERT SPENCER

"Those who, on the other hand, take an optimistic view, ... must regard as conduct to be approved that which fosters life in self and others, and as conduct to be disapproved that which injures or endangers life in self or others...

Legislation conducive to increased longevity would, on the pessimistic view, remain blameable; while it would be praiseworthy on the optimistic view." (**Herbert Spencer**, 1820-1903, *The Data of Ethics*, 1879)



"It is written: 'When you build a new house, you should make a parapet for your roof so that you bring not bloodshed upon your house should any man fall therefrom' [Deut. 22:8]....

This demonstrates, however, that there is no firmly determined time for death. Moreover, the elimination of harmful things is efficacious in prolonging life, whereas the undertaking of dangerous things is the basis for shortening life." (Maimonides, Rabbi Mosheh ben Maimon, 1135-1204, *Responsum on Longevity*)



"If you could take a man, dissect him in such a way as to balance his natures [qualities] and then restore him to life, he would no longer be subject to death"

(Abu Mūsā Jābir ibn Hayyān – a.k.a. Jabir / Geber, c. 721-815)



"There are no intellectual reasons or rules to denote the impossibility of an extended life span; therefore, we cannot deny it"

(Allameh Tabatabaei, 1904-1981)



"We must rebel against the vulnerability of the human body. ... Life is now too precious ... More than ever therefore it is urgent to overcome death"

(Fereidoun M. Esfandiary, 1930-2000, The Upwingers, 1977)

Desirability: Longevity is a pragmatic value

 Human Development Index: Longevity, Education, Income (these values are correlated)

 $HDI = \sqrt[3]{LEI \cdot EI \cdot II}.$



Longevity – The Correlate of Wellbeing

- Longevity \Leftrightarrow Education
- Longevity ⇔ Intellectual Activity
- Longevity ⇔ Prosperity
- Longevity ⇔ "Indicator of economic success and failure" (GDP/GDP per capita)
- Longevity ⇔ Equality (Gini Index)
- Longevity \IDRA Peacefulness

Objections to Extended Longevity (for the Individual)

- <u>Objections:</u>
- Diminishing change
- Spiritual and mental stagnation, boredom, lack of progress and achievement
- Prolonged suffering
- Death gives meaning to life

- <u>Counterarguments:</u>
- Stability is necessary
- Potential for learning and achievement is increased with increasing lifespan
- Suffering preventable
- Life has a meaning of its own

Life Quality and Life Quantity are Inseparable (The Centenarians are the Model)



Is extended longevity detrimental to the society?

The question of "shortage of resources" and "overpopulation"

Ethical counterarguments:

- Valuation of life overrides inconvenience
- Controlled social development preferable over blind selection
- Social solidarity and unification desirable even at some loss of resources



Empirical counterarguments – "Will Malthus continue to be wrong?"



Demographic and economic change – UK – 1960-2000

Yield of crops – kg per hectare

World (1963)

- Land and Food Requirements: ~550 people per square kilometer (over 700 if all the food comes from nutritious crops); minimal food requirement ~500 kilograms dry weight per person per year; the world dry land available for agriculture ~82 million square kilometers
- Agricultural productivity Yield of wheat in the UK (best in 1960) 3,500 kg per hectare
- Enough to feed at least 45 billion people (The Agricultural Economics Research Institute of Oxford, Clark 1963)
- Since that time, both agricultural and industrial productivity increased dramatically

Overpopulation will NOT be the result of Life Extension

- Overpopulation is the problem of countries with relatively *LOW* Life Expectancy – overcompensating for high mortality with high fertility
- Still, efforts for egalitarian development are necessary.
- Given the benefits, Longevity needs to be actively pursued.

3. Action

Given the Feasibility and Desirability – a Program for the Pursuit of Healthy Longevity is needed



The Program for the Pursuit of Healthy Longevity

From the outside:

- Gerontotechnologies (Robotics/ Assisted Living)
- Healthy Lifestyle (nutrition, exercise, rest)
- Preventive geriatrics
- Cognitive and psychological techniques
- Environmental technologies
- Improving conditions of daily life, means of access and convenience for the aged
- Social, educational and occupational integrative frameworks for the aged







The Program for Healthy Longevity

From the inside:

- Regenerative medicine: stem cells and their products, regeneration and cell death
- **Tissue engineering**
- Gene therapy: activation of sirtuins, telomerase, other "longevity genes". **Epigenetic therapy**
- Geroprotectors
- Nanomedicine
- Artificial organ replacement
- Quantified self. Data Mining





Stem cells









How do we make it?

- How do we pursue healthy life extension? What is the plan?
- How do we make it an individual and social priority?
- Who pays and for what?
- Who makes the decisions?
- How do we make life-extending technologies universally accessible?



Program for the Pursuit of Longevity -Health Policy and Research Policy Changes are needed

• <u>Possible Initial Recommendations</u>: Providing increased *funding, incentives and coordination* for academic, commercial and public organizations involved in Research and Development *to ameliorate degenerative aging processes* as the basis for future treatment of noncommunicative diseases, health care for the aged and extending healthy longevity.



 Governments should ensure the creation and implementation of the following policies to promote research into the biology of aging and aging-related diseases, for improving the health and longevity of the global elderly population

(The Critical Need to Promote Research of Aging. Aging and Disease, 6, 2015

http://www.aginganddisease.org/EN/10.14336/AD.2014.1210

• Funding:

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- Ensuring a significant increase of governmental and non-governmental funding for goaldirected (translational) research in preventing the degenerative aging processes, and the associated chronic non-communicable diseases and disabilities, and for extending healthy and productive life, during the entire life course.
 - Specifically:

• Dedicating a designated percentage of budget within relevant ministries, such as ministries of health and/or science, particularly in the divisions concerning research and treatment of non-communicable chronic diseases.

• Dedicating a specific percentage of the profits of commercial pharmacological, biotechnology and medical technology companies to such research and development.

- Establishing relevant research grant programs on a competitive as well as goal-directed basis.
- Doubling of funding for such research every 5 years for the next 20 years.

<u>Incentives:</u>

 Developing and adopting legal and regulatory frameworks that give incentives for goaldirected research and development designed to specifically address the development, registration, administration and accessibility of drugs, medical technologies and other therapies that will ameliorate the aging processes and associated diseases and extend healthy life.

• Specifically:

- Developing criteria for efficacy and safety of geroprotective therapies.
- Facilitating in silico and animal testing, and ethical safety-enhanced human testing of such therapies.
- Deploying and ensuring geroprotective therapies in the status of adjuvant and life-extending therapies.
- Providing a shortened approval pathway for therapies with high level of efficacy evidence in preclinical and early clinical trials, as well as in cases of advanced degenerative and seemingly futile conditions.
- Granting a special recognition, status and benefits to commercial and public entities engaged is such research and development.

• Institutions:

 Establishing and expanding national and international coordination and consultation structures, programs and institutions to steer promotion of research, development and education on the biology of aging and associated diseases and the development of clinical guidelines to modulate the aging processes and associated aging-related diseases and to extend the healthy and productive lifespan for the population.

Specifically:

• Establishing Biogerontology specialty and courses in Biogerontology as a common part of university curriculum.

- Developing and disseminating geroprotective regiments, based on the best available evidence, as part of authoritative health recommendations.
- Establishing cooperative centers of excellence for fundamental, translational and applied studies, alongside centers for strategic analysis, forecast, education and policy development on aging and longevity research, at academic institutes and various governmental and supra-governmental agencies.

Healthy Longevity – The Common Goal Everyone Can Help

- <u>Research</u>. Educate yourself about recent advances in longevity science, as well as its social implications.
- <u>Study relevant fields</u>, such as: bio-gerontology; geriatrics; biotechnology; medical technology; social work; regenerative medicine; nano-medicine; nutrition; ergonomics; and other fields related to healthy longevity.
- <u>Join others</u>. Discuss longevity research with friends. Organize study groups and live meetings. Join or start a network of supporters for longevity science on line.
- <u>Participate</u>, research, work, volunteer or donate for academic and public organizations involved in longevity research.
- <u>Lobby</u>. Promote legislation and policies supportive for longevity research.
- Practice a healthy, life-prolonging life-style.

http://isoad.org/

http://longevityisrael.org/

http://www.longevityalliance.org/

http://www.longevityforall.org/











INTERNATIONAL

LONGEVITY

ALLIANCE