The Age of Ageing – Can We Intervene?

Brian Kennedy
National University of Singapore
Buck Institute for Research on Aging
HEALTHSPAN vs. LIFESPAN

- Lived until 99
- Health problems at 60

- Lived until 101
- Independent whole life
LIFESPAN EXPECTANCY IS ON THE RISE


NUS National University of Singapore
LIFE EXPECTANCY THROUGHOUT HISTORY

Global Life Expectancy
-10,000 BCE - 2003

Source: Indur M. Goklany. “The Improving State of our World.” Washington, DC: Cato Institute, 2007. 36. Life expectancy is believed to have been 20-30 years prior to 1820. Age 25 is selected as an average.
SINGAPORE – POPULATION PYRAMID

1950

2010

2050
THE FACTS

• In 2050 – 9 Billion People on Earth
  • 2 Billion over 60
  • 1.6 Billion over 65
### Healthy Life Expectancy - Singapore

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in Life Expectancy</td>
<td>+ 6.0</td>
<td>+ 5.4</td>
</tr>
<tr>
<td>Change in Healthy Life Expectancy</td>
<td>+ 4.1</td>
<td>+ 3.4</td>
</tr>
</tbody>
</table>

Source: Lancet 2012; 380: 2144-62
FEWER PEOPLE TO SUPPORT SENIORS

<table>
<thead>
<tr>
<th>Year</th>
<th>Elderly Citizen</th>
<th>Citizens in working-age band of 20-64 years of age</th>
</tr>
</thead>
<tbody>
<tr>
<td>1970</td>
<td></td>
<td>![Bar]</td>
</tr>
<tr>
<td>2000</td>
<td></td>
<td>![Bar]</td>
</tr>
<tr>
<td>2011</td>
<td></td>
<td>![Bar]</td>
</tr>
<tr>
<td>2015</td>
<td></td>
<td>![Bar]</td>
</tr>
<tr>
<td>2020</td>
<td></td>
<td>![Bar]</td>
</tr>
<tr>
<td>2025</td>
<td></td>
<td>![Bar]</td>
</tr>
<tr>
<td>2030</td>
<td></td>
<td>![Bar]</td>
</tr>
</tbody>
</table>

By 2030, only 2.1 working adults will be supporting each elderly citizen

Decending Old Age Support Ratio

Source: Department of Statistics
<table>
<thead>
<tr>
<th>1990 - 2010</th>
<th>MALES</th>
<th>FEMALES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in Life Expectancy</td>
<td>+ 4.2</td>
<td>+ 1.9</td>
</tr>
<tr>
<td>Change in Healthy Life Expectancy</td>
<td>+ 2.7</td>
<td>+ 1.1</td>
</tr>
</tbody>
</table>

Lancet 2012; 380: 2144-62
## HEALTHY LIFE EXPECTANCY - RUSSIA

<table>
<thead>
<tr>
<th>1990 - 2010</th>
<th>MALES</th>
<th>FEMALES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in Life Expectancy</td>
<td>-0.1</td>
<td>+0.8</td>
</tr>
<tr>
<td>Change in Healthy Life Expectancy</td>
<td>-0.2</td>
<td>+0.7</td>
</tr>
</tbody>
</table>

LIFE EXPECTANCY BY COUNTY (USA)

http://vizhub.healthdata.org/us-health-map/
LIFE EXPECTANCY BY COUNTY (USA)

Life Expectancy

Obesity

http://vizhub.healthdata.org/us-health-map/
RISK FACTORS FOR MORTALITY

http://www.worldlifeexpectancy.com/country-health-profile
AGING IS A DRIVER OF CHRONIC DISEASE

Neurodegeneration

Cancer

Frailty

Stroke

Cataracts

Type II Diabetes

Arthritis

Heart Disease
WHAT’S HAPPENING ON THE GROUND

- Increased Assisted living / Senior Centers
- Aging in Place
- Increased hospitals / healthcare professionals
- Efforts to re-train elders
- Medical monitoring devices
- Emphasis on Rehabilitation Centers
DALYS – DEVELOPED WORLD 2010

Communicable
Non-communicable
Injuries

http://www.healthmetricsandevaluation.org/tools/data-visualizations
DALYS – DEVELOPED WORLD 1990

http://www.healthmetricsandevaluation.org/tools/data-visualizations
DECLINE IN FUNCTION WITH AGE

World Record Women's Marathon by Age

© Copyright National University of Singapore. All Rights Reserved.
CHESS RANKINGS BY AGE

Average Ranking Top Ten US Players in Age Group

- 65+: 2357
- Overall: 2782
- 13 Yr Old: 2322
- 14 Yr Old: 2400
WHAT ABOUT KEEPING PEOPLE HEALTHY LONGER?

IGNORE  MANAGE  PREVENT
WHAT ABOUT KEEPING PEOPLE HEALTHY LONGER?

IGNORE MANAGE PREVENT REVERSE?
A PIPELINE FOR HUMAN AGEING INTERVENTION

Discovery
- Yeast
- Worms
- Flies

Conservation in mammals
- Mice

Validation in Humans
- Biomarkers / Healthy Ageing
- Early Stage Disease

Implementation
- Primates? Dogs?
## Lifespan Extension Agents

### Behavioral
1. Calorie Restriction
2. Exercise
3. Intermittent Fasting
4. Alcohol

### Small Molecules
1. Rapamycin
2. Metformin
3. NSAIDs
4. Acarbose
5. STACs (Resveratrol)
CALORIE RESTRICTION IN MICE AND RATS

ANIMAL PROTEIN INTAKE AND MORTALITY

All-Cause Mortality

Predicted Time till Death

Low Protein  Moderate Protein  High Protein
The on-going “Stanford Runners Study”
Started in 1984 assessing mortality & morbidity in runners v. non-runners
Alcohol Dosing and Total Mortality in Men and Women

An Updated Meta-analysis of 34 Prospective Studies

Augusto Di Castelnuovo, ScD; Simona Costanzo, ScD; Vincenzo Bagnardi, ScD; Maria Benedetta Donati, MD, PhD; Licia Iacoviello, MD, PhD; Giovanni de Gaetano, MD, PhD

Conclusions: Low levels of alcohol intake (1-2 drinks per day for women and 2-4 drinks per day for men) are inversely associated with total mortality in both men and women. Our findings, while confirming the hazards of excess drinking, indicate potential windows of alcohol intake that may confer a net beneficial effect of moderate drinking, at least in terms of survival.

Figure 1. Relative risk of total mortality (95% confidence interval) and alcohol intake extracted from 56 curves using fixed- and random-effects models.
LIFESPAN EXTENSION AGENTS

**BEHAVIORAL**

1. Calorie Restriction
2. Exercise
3. Intermittent Fasting
4. Alcohol

**SMALL MOLECULES**

1. Rapamycin
2. Metformin
3. NSAIDs
4. Acarbose
5. STACs (Resveratrol)
RAPAMYCIN IS DOSE DEPENDENT

Rapamycin-mediated lifespan increase in mice is dose and sex dependent and metabolically distinct from dietary restriction.
RAPAMYCIN AND AGE-RELATED DISEASE

Neurodegeneration

Cancer

Frailty

Stroke

AMD

Type II Diabetes

Arthritis

Heart Disease

• At doses relevant to disease treatment and lifespan extension, rapamycin has shown to
  – Affect metabolism: Glucose intolerance, insulin resistance, glucose homeostasis
  – Present other side effects: lipid dysregulation, stomatitis

• Significantly limits therapeutic potential of rapamycin & analogs

Table 1 mTOR inhibitors—summary of toxicities

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades (%)</td>
<td>Gr 3/4 (%)</td>
<td>All grades (%)</td>
</tr>
<tr>
<td>Mucositis</td>
<td>20–75</td>
<td>1–4</td>
<td>40–44</td>
</tr>
<tr>
<td>Skin rash</td>
<td>47–76</td>
<td>4</td>
<td>25–29</td>
</tr>
<tr>
<td>Pulmonary toxicity</td>
<td>2–36</td>
<td>9</td>
<td>8–14</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>26–89</td>
<td>17–16</td>
<td>50–57</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>21–87</td>
<td>1–21</td>
<td>76–77</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>21–83</td>
<td>3–4</td>
<td>71–73</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>13–49</td>
<td>13–18</td>
<td>32–37</td>
</tr>
<tr>
<td>Anemia</td>
<td>29–45</td>
<td>9–20</td>
<td>91–92</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>14–40</td>
<td>1–8</td>
<td>20–23</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>7–19</td>
<td>3–5</td>
<td>11–14</td>
</tr>
<tr>
<td>Asthenia/fatigue</td>
<td>38–51</td>
<td>8–11</td>
<td>31–38</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>20–21</td>
<td>0</td>
<td>7–10</td>
</tr>
</tbody>
</table>

* Reported as dyspnea in most trials. b Reported either as fatigue or asthenia

Soefje et al., Targ Oncol (2011) 6:125–129
CLINICAL STUDY OF HEALTHY PEOPLE OVER 65 WITH RAPALOG

- Limited exposure at low, medium and high dose, followed by influenza vaccination to measure immune response

- Side Effects - Not above background at low and medium dose, significant at high dose

- Improved immune response at all three doses

- Improved response to heterologous virus

TRIALS IN DOGS
A Single *IGF1* Allele Is a Major Determinant of Small Size in Dogs

Nathan B. Sutter,1 Carlos D. Bustamante,2 Kevin Chase,3 Melissa M. Gray,4 Keyan Zhao,5 Lan Zhu,6 Badri Padhokasahasaram,7 Eric Karlins,3 Sean Davis,1 Paul G. Jones,6 Pascale Orignon,1 Gary S. Johnson,2 Heidi G. Parker,1 Neale Fretwell,8 Dana S. Mosher,1 Dennis F. Lawler,9 Ebenezer Satyaratj,9 Magnus Nordborg,9 K. Gordon Lark,7 Robert K. Wayne,6 Elaine A. Ostrander10

Sutter et al. 2007 Science
RAPAMYCIN TRIAL IN COMPANION (PET) DOGS

- Larger-breed dogs with average lifespan ~8-12 years
- Start **low dose** rapamycin at 6-9 years
  - Minimal if any side effects
- Follow healthspan parameters and survival in treated and untreated animals for 3-5 years
- Prediction: Treated animals will be healthier and have lower mortality than untreated animals

[www.dogagingproject.com](http://www.dogagingproject.com)
METFORMIN

• Trade name – Glucophage
• FDA approved – Type II diabetes, Non-alcoholic fatty liver disease
• Suppresses glucose production in liver, enhanced peripheral glucose uptake
• Millions of people have taken it
METFORMIN – A RETROSPECTIVE STUDY

(c)

Cumulative survival

Time to death (years)

- Metformin monotherapy
- Sulphonylurea monotherapy
- Controls (matched with metformin)
- Controls (matched with sulphonylurea)
THE GOAL OF TAME IS LINKING GEROSCIENCE TO DISEASE REDUCTION

FDA: What would we need to show in a clinical trial that would allow the FDA to approve a new indication for metformin for “delaying multiple morbidities relating to aging”?

NIR BARZILAI
MAIN GOAL

EXTEND HUMAN HEALTHSPAN IN SINGAPORE

• Identify and de-risk interventions
• Test in healthy ageing people (or early stage disease)
• Develop implementation plans for Singapore
HEALTHSPAN vs. LIFESPAN

PRESENТ
Birth  Morbidity Onset  Death

EXTEND
Birth  Morbidity Onset  Death

EXTEND
Birth  Morbidity Onset  Death

COMPRESSED
Birth  Morbidity Onset  Death

HEALTHSPAN
LIFESPAN
SG90 Longevity and SG60 Healthspan Cohorts

SG90 Longevity Cohort (n=1,000 ≥85-year-olds)

About 200 ≥85-year-old subjects with exceptional health span

SG60 HealthSpan Cohort (n~1,500 ~60 years of age)

Offspring of SG90 subjects with exceptional health span (n~500) and the spouses of these offspring (n~500)

Strategy: Study & compare the present, look back at the past. Predict the future.

Unrelated controls age- and gender-matched to the Offspring (n~500)
Healthspan Intervention Studies

**Human Intervention Testing Program (HIP - short-term studies)**

- Screening
- 10-week Treatment A
- 4-week WASHOUT
- 10-week Treatment B
- 4-week WASHOUT
- Screening
- Biological/Biomarker Outcomes

**Randomised Controlled Trials (medium-term studies)**

- Screening
- 3-5 years Intervention
- Clinical Outcomes
- Screening
- 3-5 years Control
- Clinical Outcomes

Groups:
- Young
- Healthy
- At-Risk Aging
EMERGING APPROACHES

• Nutritional Supplements
  - NAD Precursors
  - TCM
• Factors in Young Serum
• Drug Development
  - Senolytics
• Gene Therapy
  - Telomere Extension
• Longevity Clinics
• Medical Diets
POSSIBLE BIOMARKERS

- Epigenetic Clock
- Metabolomics
- p16INK4A protein levels
- Inflammatory Markers
- Microbiome changes
- Telomere length
- Functional markers (walking speed etc.)
- Systems Approaches
FOUR KEYS TO LONGER HEALTHSPAN

• Healthy Diet
• Exercise
• Mindfulness
• Quality Sleep
Silver Tsunami?

or

Golden Opportunity?
THANK YOU