BIOLOGY OF AGING AND THE PROMISE OF HEALTHSPAN EXTENSION

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Learning Objectives:
- Distinguish between different methods and mechanisms of longevity extension.
- Compare and contrast their effects on lifespan and Healthspan.
- Evaluate practical applicability of different longevity extension treatments.

DISCLOSURE OF COMMERCIAL SUPPORT
Janko Nikolich-Zugich, MD, PhD does have a significant financial interest or other relationship with manufacturer(s) of commercial product(s) and/or provider(s) of commercial services discussed in this presentation.

Other: Organic Vaccines, Inc., Scientific Advisory Board
Imagine.....

A world with no frailty
A world where infections are not scary for older adults
A world where people live healthy and productive lives into their 100’s

You are sharing our vision!

What Does the Arizona Center on Aging Do?

We Teach

We Provide Care

We Discover

A center that spans everything from fundamental bench research to community outreach and models of care.

Biology of Aging..... or:

Why do our bodies grow old...and what can we do about it?
Two simple points

Point One
The biology-of-aging promise: “change the face of aging.”
- Live to about 112 years
- Spend 111 of those being healthy.

Point Two
To deliver upon this promise we cannot think as usual.
We have to invest in the prevention of age-related disability in the whole body (and mind).

What would it mean to change the face of aging?
Not the eradication of aging, nor the prolongation of suffering
but the prolongation of normal, vital function and quality of life...
vigorous and vibrant activity and a greatly shortened period of functional decline.
What would it mean to change the face of aging?

Health-related Quality of Life
- Absence of distressing physical symptoms
- Emotional well-being
- Functional status (daily living and pleasurable activities)
- Quality of close interpersonal relationships
- Enjoyment of social activities
- Satisfaction with care
- Sexuality, body image and intimacy
- Mental health

Biological aging vs. psychosocial aging

Experience  | Function  | Older adults as a societal resource!
---|---|---
Years  |  | 

Early development is highly and precisely regulated

Juvenile Form  
Mature Adult Form
Biological aging is what happens as the rules weaken and expire

Why do we age at all?

- Some genes do **good things early**, but **bad things late**. Genes needed for rapid growth can cause cancer later

- Other genes do **bad things**, but are **controlled early**. When controls weaken, their effect is felt. *Alzheimer's, cataracts, osteopenia, immune decline, etc.*

Basic questions
Nearly all mammals age in similar ways but lifespan among mammals varies 30-fold.

Caloric restriction (~33% reduction in calorie intake) extends rodent lifespan 40%. Animals are healthy, active and devoid of the most frequent diseases of aging. At least ten single gene mutants can extend mouse lifespan by 20-50%; most show better health.

The same intervention (Caloric restriction) and the same genes (insulin/insulin growth factor receptor pathway) control the aging/function in the same manner in some very distant cousins.
Really, why do we age?
Questions that a theory of aging must answer.

- Why do organisms get less resilient as they get older?
- Why do some species take 70+ years, but others, closely related, take only 3 years to age?
- Why do bad things happen to multiple cell and tissue types pretty much all around the same time?
- Why is aging slowed by some interventions (caloric restriction; attenuation of insulin/IGF signaling, etc.)?

Some proposed theories of aging

- Oxidative stress
- Glycation stress – too much sugar
- Exhaustion of dividing cells (Hayflick)
- Telomere shrinkage (neo-Hayflick)

Progress: *Metabolism and Stress Theory*

Nutrient-energy mis-sensing

Nutrient-energy dysbalance leads to reduced resistance to various forms of stress/damage.

If you (your cells) can deal with damage you will age well.
The turning point in aging research

Mutations that make worms long-lived also make them hard to kill

Source: From R. Miller. Data: Johnson, Lithgow, Murakami, Luan, others

Some mice live 40% longer and age slower: growth factor sensing is weaker

Source: Murakami, et al. 2003

Why is this important?

• Long-lived worms, flies and mice are resistant to many kinds of stress.
• The stress resistance might be the cause of the successful aging.
• The connection goes way back in evolution.
“Stress resistance and longevity” genes code for hormones shared by many


The main challenge for the biology of aging

To work out the pathways by which single genes (enzymes/hormones) and simple interventions radially improve a complex process of aging

and then to scientifically determine...

• Can we do this in humans? (safety)
• Would this improve human healthspan? (efficacy)
• Should we do this in humans? (ethics, socioeconomics, etc.)
The U.S. population continues to grow older

Healthspan

Older adults living active, independent lives with self-reported good health and satisfaction

Unfortunately, not all enjoy a great healthspan...
10% of sickest, frailest Medicare patients account for over 60% of total spending.

And they receive poor care!

Moreover, if we continue with business as usual, we lose an irreplaceable resource of wisdom, experience and energy,

or...

What we want  What we get
Immediate help: new models of care

Our healthcare delivery system must change:

• Team-based home care
• Telehealth

Project Leaders: Mindy Fain, Jane Mohler (Arizona Center on Aging)

Real long-term help: biology of aging

Even with the greatly improved healthcare delivery system, the model is not sustainable. So in addition, we must increase healthspan.

The elephants in the room:
Building a world and healthcare system where we can grow old

Ageism: an “ism” that must be addressed

Older adults as a societal resource!

The promise of aging research

Return the vast wisdom, experience and energy to the society by enabling long and strong involvement of older adults in the society.
Or,
what if we figured out how these genes and diets worked and then used this information to change the face of human aging?

What we cannot do and why

Interventions too impractical to worry about:
• Genetic alterations before birth
• Genetic alterations of adults
• Caloric restriction

What we could achieve

Realistic longevity projections:
• Caloric restriction increases lifespan 30-45%
• Other interventions increase lifespan 28-60%
• Thus, a defensible, evidence-based estimate is a lifespan increased by about 40%.

The equivalent human lifespan (mean):
~112 years (111 healthy) i.e., Living Beyond 100
Living Beyond 100

Can’t we just cure the diseases of aging?

Deaths per 100,000 per year

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<tr>
<th>23</th>
<th>35</th>
<th>45</th>
<th>55</th>
<th>65</th>
<th>75</th>
<th>85 Years</th>
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<td>10,000</td>
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<td>100</td>
<td>10</td>
<td>1</td>
<td>0.1</td>
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Main causes of death in the U.S.: 1997
- Heart disease
- Cancer
- Stroke
- Emphysema
- Accidents
- Pneumonia
- Diabetes
- Kidney disease
- Alzheimer’s

Living Beyond 100

The whole-organism-based approach

Today: The average woman lives to 81

- Cure cancer
- Cure heart disease
- Cure cancer + heart disease
- Cure cancer + heart disease + stroke + diabetes

Delay aging

Aging is viewed (incorrectly) as unalterable

• A scientist/politician/public figure who wants to “conquer cancer” = a hero.
  A scientist/politician/public figure who wants to “slow aging” = a nut-case.

• Drugs purported to slow aging are highly profitable even though they don’t work

Why haven’t we changed aging yet?
Why haven’t we changed aging yet?

• It’s not *that* easy to find age-changing drugs/treatments safe and effective for humans
• but much of this has to do with a lack of funding for aging-altering research (beyond mice).

Federal funding

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<th>Total NIH funding</th>
<th>National Institute on Aging</th>
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<tr>
<td>NIA Biology Program</td>
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Living Beyond 100

Federal funding

Conclusions

1. Our investment into poor health care for older adults is huge; our investment into changing the face of aging is ridiculously small.

2. Our society is good at reacting to crisis (e.g. curing a monster disease) but not at preventing it (making sure the disease does not occur in the first place). Often, this is neither smart nor economical. Can we change?

Quiz: Would you fund this science?

We have an empirical treatment that diminishes by 90% the risk of breast cancer in aged rats.

It does have some side effects, and they are all good. For example, it also diminishes cataracts, cognitive decline, other cancers, immune failure, kidney disease, etc.

It leads (in animal models) to lifespan extension about 10-times that predicted from a cure for cancer.
Living Beyond 100

The current situation, as viewed from the swamp

“We are confronted with insurmountable opportunities. We have met the enemy, and he is us.”

Late-life intervention: Rapamycin at last third of life increases lifespan in mice

Survival

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<th>Control</th>
<th>Rapamycin</th>
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<td>Pooled females p &lt; 0.0001</td>
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0 200 400 600 800 1,000 1,200 Age in days

What to do next?

What’s the best Rapamycin dose?
Does in work on dogs? Monkeys?
How are people on Rapa trials (for cancer) doing for aging?
Are some of its targets ‘good’ and others ‘bad’?
Are there other drugs like Rapa, but safer?
Does it produce serious side effects at these doses?

Team members: T. Price, K. Limesand, H. Brooks, S. Ghosh and E. Goldberg, Arizona Center on Aging, CoM, CALS

Source: Randy Strong, Nancy Nadon, Dave Harrison, Dave Sharp, et al., Nature 2009
Shocking news!

No vaccine has ever been engineered to work in older adults!

Working on immune rejuvenation

For those who have lost most of the necessary T and B cells, we need to kick-start the lymphocyte production factory.

Young

Old

Rejuvenated

Where we stand today...

“...and for the mice in the audience, I have some wonderful news!”

Pedro Lowenstein
Living Beyond 100

Get involved.

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