“All men are cremated equal.”

-Spike Milligan
In late 2013, sofosbuvir in combination with ribavirin was approved by the FDA. This combination yielded a ~95% cure rate in HCV genotype 2 infections.
“Quietly, over the past few decades, remarkable discoveries have been made about the biology of ageing.”

-Cynthia Kenyon, Calico LLC
The following article was published in one of Britain’s largest newspapers called The Telegraph on November 29, 2015:

World’s First Anti-Ageing Drug Could See Humans Live to 120

By Sarah Knapton
Four million years produced an 11-year increase from 20 to 31

115 years produced a 41 year increase
WHAT IS AGEING?

When wear and tear outruns repair.
An organism is considered to display negligible senescence if it does not exhibit any measurable decline in survival characteristics such as strength or mobility with age, does not have a gradually increasing death rate with age, and also does not exhibit any measurable reduction in reproductive ability with age.
VERTEBRATE OF THE YEAR 2013!
AGEING IS VERY COMPLEX

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AGEING THEORIES

- Disposable Soma
- Oxidative Theory of Ageing
- Evolutionary Theory of Ageing
- Second Law of Thermodynamics
- Rate of Living Theory

Antagonistic Pleiotropy + Hyperfunctioning
MODELS OF AGEING
*Depending on level of caloric restriction

Source: Journal of Nutrition, April, 116(4), pages 641-54.
Age is the single biggest risk factor in the deadly quintet of diseases accounting for 70% of all deaths.

Source: Figures for United States - 2014
THERAPIES IN DEVELOPMENT

afar
ELYSIUM
restORbio
UNITY
AGEX THERAPEUTICS
Elevian
LYGENESIS
Eating consistently less without starvation and malnutrition

 Increases life expectancy and lessens disease burden in aged mammals but unclear whether findings translate into humans

 CR mimetics being investigated include resveratrol, oxaloacetate, rapamycin, rimonabant

 CR increases the production of keytone bodies that are produced when liver uses fat stores rather than sugars – e.g. ketogenic diet

 Mimetic of ketogenic diet is beta-hydroxybutyrate

 Certainly makes life FEEL a lot longer!
• 60 year old drug derived from French Lilac
• Excitement - diabetics taking metformin showed 15% mortality advantage over matched non-diabetic population
• Targeting Ageing with Metformin (TAME) – first FDA approved trial looking at delaying onset of age related diseases
• Nir Barzilai, Albert Einstein College of Medicine is proponent of the TAME trial
NAD+ PRECURSORS

• NAD+ (Nicotinamide adenine dinucleotide) - coenzyme found in all living cells that decreases with age
• NAD is a critical co-factor, or helper molecule, to a family of proteins called sirtuins
• Two approaches:
  – Increase NAD+ in cells
  – Prevent decline in NAD+ - CD38 inhibition
• Eric Verdin, President and CEO of the Buck Institute for Research on Aging a key opinion leader in this area

A Potent and Specific CD38 Inhibitor Ameliorates Age-Related Metabolic Dysfunction by Reversing Tissue NAD+ Decline
- Rapamycin is the only compound to extend life in all species studied to date
- Being tested in middle aged dogs in the Dog Aging Project
- Advanced human clinical trials being run by resTORbio (NASDAQ:TORC)
- phase 2b clinical trials with RTB-101 in combination with everolimus (a rapalog)
  - Enhanced response to influenza vaccine by ~20%
  - Ameliorated immunosenescence in elderly volunteers
  - Reduced % of CD4 and CD8 T lymphocytes expressing PD-1 receptor, which inhibits T cell signalling
Cellular senescence – Phenomenon by which normal cells cease to divide – Dormant but metabolically active state – Promotes inflammation and accelerates ageing

Leonard Hayflick observed replicative senescence in 1960s – the Hayflick Limit

Caused by endogenous and exogenous DNA damage

Senolytic drugs increase maximum lifespan by 35% in mice
Targeting senescent cells increases bone mass.
• Cardiac hypertrophy
• Kyphosis (curvature of spine)
• Loss of subcutaneous fat
• Reduced locomotion
• Cancer

• Live ~35% longer
• Dramatic extension of health span
• Oldest known attempt to extend lifespan
• Circulatory systems of animals surgically joined
• Used by Kim Il Sung to the extent it changed his blood type from AB to B; he died age 82
• Modern version looks at specific “factors” in blood that provide the benefits and administering by transfusion
• Ambrosia sells blood from younger people for USD 8,000 a pop!
**Autophagy**

- Cellular disposal system that clears unwanted components to lysosome such as dysfunctional mitochondria
- System becomes less efficient with age
- Mice with high expression of autophagy-associated protein beclin-1 live 10% longer, and have a lower incidence of cancer and heart disease than wildtype
- Metformin induces autophagy under certain conditions
- Inhibition of CoX7a1 leads to increased autophagy
WNT Pathway

- Wingless-related integration site
- Signalling pathway that regulates self-renewal and differentiation of adult stem cells
- Dysregulation of WNT in a specific tissue almost always leads to disease
- Implicated in cancer and degenerative conditions
- Significant capital raised by Samumed (US $12b private market valuation) with lead indications in osteoarthritis and alopecia

FOXO

- Forkhead box family of transcription factors
  - FOXO1 – insulin signalling
  - FOXO3 – tumour genesis
  - FOXO4 – Judith Campisi
- Play a role in expression of genes involved in cell growth, proliferation, differentiation and longevity
- Believed to contribute significantly to the immortality of the hydra
- Evolutionarily conserved in humans
2020
AI based medical diagnostics & therapy recommendations are used in the majority of US healthcare

2028
Robots will have real relationships with people, supporting care of aging, personal hygiene and food preparation. Sex bots become popular.

2030
Humanity has achieved “Longevity Escape Velocity” for the wealthiest

2032
Medical nanorobots demonstrated in humans are able to extend the immune system.

2036
Longevity treatments are routinely available and covered by life insurance policies, extending the average human lifespan 30 – 40 years.
**INDUCED TISSUE REGENERATION**

**Cox7a1 Gene:**
- Expression after the embryonic-foetal transition inhibits regeneration of organs
- Not expressed in liver which allows it to regenerate
- Inhibition leads to reversion to embryonic state and increased autophagy
- 90% of cancers inhibit its expression
- Mexican salamander stuck in developmental larval state does not express
• Lygenesis, Inc. novel technology to use lymph nodes as mini-bioreactors

• When lymph nodes are seeded with purified hepatocytes (liver cells), the cells engraft and grow into small, functional ectopic livers

• Livers only grow to size required by body

• Bridge patients to transplant or completely supplanting the need for a transplant

• Applications in other organs including the thymus and pancreas
GENE THERAPY
WHAT DOES THIS ALL MEAN?
Gone are the days when you’re born, learn, earn, burn out, retire and expire!
"I finally put something aside for my retirement. I put aside my plans to retire."
• Plateau and decline
• In 2015, 46% of world’s pop. (in 86 countries) below replacement level of 2.1
• 2017 – 2050
  – half the world’s population growth will occur in 9 countries
• “Peak Children”
  – 1960 / 1 billion / 35%
  – 2011 / 1.9 billion / 27%
  – 2050 / 1.9 billion / 20%

Source: UN World Population Prospects
"I’ve crunched the numbers in your retirement account. It’s time to figure out who will be wearing the mask and who will be driving the getaway car.”

**INDUSTRIES TO BE DISRUPTED**

- Pensions
- Life insurance
- Healthcare – BUT burden of care likely to decline
- Leisure industry
- Social care
- Education
Computing

Internet

Longevity
Global drug spend to hit USD $1.4 trillion in 2020
Long Road to Approval

4.5 years Discovery
5-10,000 potential drugs are investigated if a pharma firm is seeking treatment for a condition and doing the work is in-house.

1 year Testing and Improving
Thousands of potential molecules are whittled down to the most promising 10-20 drugs or ‘leads’. Sometimes companies buy in promising drugs from scientists who have done the basic work.

1.5 years Clinical trials
After thorough testing in the lab, 5-10 drugs are taken forward into the first in-human trials.

1.5 years Clinical trials (Phase 2)
2-5 drugs show promise in patients and are taken forward into larger trials.

2.5 years Clinical trials (Phase 3)
1 or 2 drugs work well enough to go into late-stage clinical trials.

1.5 years Drug approval
1 drug is shown to have an effect on the disease.

Drug approved for patients

How long does a new drug take to develop?
Pharma says 12.5 years. Critics say the work is often supported by public funds.
MARKETS DEVELOP QUICKLY

Cancer Immunotherapy

Revenue per year

Source: GBI Research

Biologics

Revenue per year

Source: Grand View Research
TOTAL ADULT POPULATION

GLOBAL MEDIAN INCOME

GLOBAL MARKET FOR LONGEVITY

5.70 BILLION

$9,733 PER YEAR

$312 BILLION PER YEAR

~15%

EARN MORE THAN

@ $1 PER DAY
Founded by Jim Mellon, Greg Bailey and Declan Doogan
Highly experienced investors, entrepreneurs and drug developers
Combination of artificial intelligence and classical drug development
Company has raised US $63m to date – US $50m Series A
Contemplating IPO in 2019

Portfolio and collaborations includes:
- Insilico Medicine, Inc.
- Juvenescence AI
- NetraPharma
- Lygenesis, Inc.
- AgeX Therapeutics, Inc.
- Buck Institute for Research on Aging

Multiple deals in pipeline
The market for anti-ageing treatments is currently worth USD 140 billion annually.

Imagine how much they’ll be worth when they actually work.