Peter Attia MD Keypoints — Longevity & the Biology of Aging

Peter Attia MD Keypoints

Episodes in this pack: 31

359 How metabolic and immune system dysfunction drive the aging process, NAD, aging clocks, & more

Guest: Eric Verdin
Date: 2025-08-04 · Duration: 2:31:47
URL: https://www.youtube.com/watch?v=818-8vS5JpA

KEYPOINTS

• The immune system and brain may set the pace of whole-body aging

Verdin points to work from Tony Wyss-Coray's lab finding that aging markers for the brain and immune system best predict lifespan. Both are spread throughout the body. In mice, removing the DNA-repair gene ERCC1, or causing mitochondrial dysfunction, only in immune cells speeds up aging and senescence in every organ. Whether this holds in humans is 'the million-dollar question.' Peter adds the endothelium; Verdin sees barrier function (blood vessels, skin, blood–brain barrier) as a key target.

• The oxidative-stress theory isn't dead just because antioxidants failed

Electrons leak from the mitochondrial respiratory chain and form reactive oxygen species, and the leakage grows with age. Vitamin C and E trials failed, but Verdin says these molecules also do useful signaling: blunting them can blunt the benefits of exercise. Peter adds that the trials never had a good marker to show the antioxidants actually reduced free radicals. Martin Brand at the Buck found that blocking some production sites helped and blocking others didn't; that program was dropped.

• Fuel choice matters, and glucose is the 'dirtiest' fuel

Verdin ranks beta-hydroxybutyrate as the cleanest fuel, then fatty acids, with glucose worst. Mice fed pure fat that never saw a carbohydrate lived longer, though Peter notes most 'high-fat' mouse diets are really high-fat, high-sugar 'donuts.' Many ITP drugs that extend life (acarbose, canagliflozin, and metformin combined with rapamycin) act on glucose. Verdin's main suspect is the insulin and IGF-1 spikes from fast-absorbing carbohydrate, and he uses CGMs to flatten them. He found a ketogenic diet socially isolating and is developing a ketone ester.

• When it comes to glucose and blood pressure, lower is usually better

Peter cites data in non-diabetics showing all-cause mortality falls steadily as A1C goes down, with no lower limit found, so 5.0 beats 5.6 even though both count as 'normal.' Verdin's own doctor dismissed his creeping fasting glucose of 96. Both say blood pressure of 105/65 beats 115/70 if you have no symptoms. BMI is crude: Peter is 'overweight' by BMI at 11% body fat, and Verdin estimates that about 20% of overweight people are metabolically healthy, though he worries about the long term.

• Immune decline is the 'fifth horseman'

Peter says he should have added immune health to the four horsemen in Outlive. During COVID everyone could be infected, but people over 75 had about 84-fold excess mortality. Flu and RSV follow the same pattern. Verdin explains innate immunity (fast, non-specific, no memory) and adaptive immunity (T and B cells that expand and leave memory cells). In his recollection, vaccine response drops to about 30% after 70. The two of them couldn't square that with how protective COVID vaccines seemed in the very old, and left it for the show notes.

• The thymus shrinks early, and growth hormone is a double-edged sword

After about 50 the thymus is mostly fat, so few new naive T cells are made. Small growth hormone studies in HIV patients, and later the Fahy TRIIM trial (GH plus low-dose metformin and DHEA), suggested some thymus regrowth. Peter calls GH the only active ingredient. Verdin worries GH causes glucose intolerance, and notes that bigger dogs, driven by GH, live shorter lives, as do taller people. Peter says every patient he has seen on GH feels better, but testosterone is far better against sarcopenia.

• Rapamycin: dose and timing separate immune suppression from immune benefit

Joan Mannick's 2014 trial (as Peter recalls it, 300+ people over 65 in four groups) found that 5 mg weekly boosted vaccine response about as well as 20 mg, with fewer side effects. Verdin took 4–6 mg weekly and got a pimple on his nose the next day, so he was clearly briefly immunosuppressed. He stopped because he noticed no benefit. He questions ITP results because lab mice live shorter than their size predicts, have high growth (mTOR) drive, eat poor chow and live sterile, sedentary lives. He would advise a 40-year-old against rapamycin.

• NAD decline seems driven by CD38, and supplements may just pour water into a leaky sink

NAD is used by 600+ enzymes, plus sirtuins and PARPs. Eduardo Chini showed that mice without CD38 don't lose NAD with age and live about 15% longer, though Verdin suspects that isn't only because of NAD. Factors released by senescent cells (the SASP) increase CD38 in macrophages. CD38 also breaks down NMN, pushing excess nicotinamide into methylation, which drains the methyl-donor pool and raises homocysteine. Recycling is so fast that blocking it empties a cell of NAD in four to six hours.

• Epigenetic clocks aren't ready for clinical use

Clocks can swing about five years with time of day. Matt Kaeberlein's duplicate samples disagreed within and across clocks. Blood mixes 500+ cell types: Verdin's lab found naive T cells look 20–25 years younger than memory T cells, so infections that expand memory cells fake 'accelerated aging.' His 'IntrinClock' excludes those sites and doesn't move with COVID, HIV or the GH trial. He favors DunedinPACE for tracking response to interventions. Peter notes no clock yet predicts lifespan better than chronological age.

EXAMPLES

• Verdin on tirzepatide

As a self-experiment, not an endorsement: A1C fell from 5.4–5.5 to 5.0 and fasting insulin to 5, with six to seven pounds lost and no muscle loss while exercising. After two weeks he felt full for the first time in his life. Peter suggests an oral glucose tolerance test with insulin.

• 1 g of NMN doubled his homocysteine

It rose from about 7 to 15 and took three to six months to return to 7–8 after he stopped. Peter suggests trying TMG. Lab animals typically get about 10 times typical supplement doses.

- **Intravenous NAD**
  NAD hardly exists in plasma and is too big to enter cells. A study cited by Verdin shows the liver mostly converts infused NAD into nicotinamide, which is cheap at a pharmacy, versus about $700 an infusion. He has heard anecdotes of striking motor improvement in Parkinson's but calls them unstudied.
- **Organ-specific proteomic clocks**
  Wyss-Coray's UK Biobank work (40,000+ people) uses organ-specific blood proteins to flag a struggling organ. Verdin sits on the board of the startup. Peter worries about false positives, as with whole-body MRI and thyroid nodules.
- **IL-11 blockade**
  Blocking IL-11 in mice extended life. Verdin frames chronic innate immune activation in response to accumulated damage as 'Jekyll and Hyde': it helps repair, but it also depletes NAD and harms stem cells.

OTHER RELEVANT

- **Exercise first**
  Verdin calls exercise in all its forms the one proven anti-aging intervention. It also improves vaccine and infection responses. Optimize it before adding drugs.
- **If you take NAD precursors, keep doses modest and track homocysteine**
  Verdin's former approach was about 250 mg each of NR and NMN, possibly reasonable at 60+. Be cautious if you might have an early cancer: animal data hint precursors could speed tumor growth, and raising NAD may feed the SASP.
- **Be skeptical of tests sold alongside fixes**
  Both say to run from a company selling an unvalidated test and the supplement to 'correct' it. Only order tests whose results would change what you do.
- **Check your titers**
  Verdin, born in 1957, had his measles titer checked to see whether he needed revaccination. This is a simple routine way to assess specific immunity.

357 A new era of longevity science: models of aging, rapamycin trials, biological clocks, & more

Guest: Brian Kennedy
Date: 2025-07-21 · Duration: 2:12:32
URL: https://www.youtube.com/watch?v=7yNvz_0Q1eQ

KEYPOINTS

- **The 'hallmarks of aging' are readouts of one connected network, not 12 separate targets.**
  Kennedy, former CEO of the Buck Institute and now running about 35 PIs in Singapore, wrote the 'pillars of aging' companion review and drew lines connecting all the pillars. Interventions like rapamycin improve every hallmark at once. Healthy aging means a homeostatic network that stays responsive. Fixing hallmarks one by one won't work.
- **Inflammation keeps emerging as central—and baseline mTOR creeps up with age.**
  Almost every lifespan-extending intervention reduces chronic inflammation, and inflammation dominates the main components of his lab's aging clocks. Baseline mTOR rises in aging stem cells, losing the dynamic range to switch on for a wound or meal and off otherwise. Elevated mTOR feeds chronic inflammation, which feeds mTOR. Good interventions restore youthful range rather than push anything supra-physiologic.
- **Aging looks like linear damage plus an oscillating 'how well you're coping' component.**
  Breaking UK Biobank-type data into principal components, one aging component rises linearly—'damage' or accumulated stochastic change. Another oscillates around it with illness, behaviour and drugs. Nearly all current interventions, including everything in Attia's book, act on the oscillation. Kennedy says that could mean 5–10 extra healthy years—'a revolution'—but probably not 150-year lifespans.
- **The 'valley' resilience model explains exponential mortality from linear damage.**
  Following Peter Fedichev's work at Gero, health is a ball in a valley. When young the walls are steep, so you're pulled back after junk food or illness. Damage lowers the hills, so the chance of tipping into a failure state rises exponentially, consistent with Gompertz mortality. With about 50 possible failure states, treating one disease barely helps; you must keep all the hills high.
- **Bending the slope may need new kinds of interventions, such as lowering system 'noise' or reprogramming.**
  Kennedy wonders whether we should target noise—such as transcriptional noise—rather than how long worms live, since worms are already in a failure state. He expects fitness trade-offs, which timing might avoid. Long-lived yeast mutants mostly wouldn't survive in the wild. Partial reprogramming could replace damaged cells but is early. He's returning to basic discovery science for this.
- **Methylation clocks are overhyped as causal; many data types make equally good clocks.**
  Proteomic, microbiome and facial-structure clocks (Jackie Han's facial clock rivals methylation) also predict age; association isn't causation. In NHANES with about 200 months of follow-up, some first-generation methylation clocks predicted mortality worse than chronological age. GrimAge and PhenoAge beat it. Matt Kaeberlein's eight simultaneous commercial tests disagreed even with identical repeats.
- **A ~50-marker routine-lab clock beat every other NHANES predictor of death, and it's actionable.**
  About 30 of the markers come from a complete blood count; the rest are standard labs, inflammatory markers and a few self-reports, costing about $300 in Singapore. It outperformed ASCVD risk scores. Principal components flag fixable drivers, such as four in-range markers adding about four years of biological age, roughly 50% higher mortality risk. At 65 in NHANES, about 20% of people needed but lacked treatment, and well-controlled people on medication aged slower than those who needed none.
- **Rapamycin remains the gold-standard small-molecule geroprotector, but probably with modest human effect.**
  Weekly dosing that lets trough levels fall likely avoids immune suppression and may even protect against respiratory infection, as Mannick's trials suggested. Kennedy expects it to extend healthy years rather than change the damage slope. His Singapore trial gives about 5 mg weekly for six months to 150–200 healthy 40–60-year-olds, measuring clocks, cytokines, pulse-wave velocity, DEXA, strength and cognition. Attia doubts most of those endpoints will move.
- **Combining many supplements is more likely to cancel out than add up.**
  In mouse combination studies Kennedy sees interference more often than synergy—'mixing 20 colours of paint' gives grey. He adds one compound at a time and measures before and after. With $100 million a year instead of about $4 million, he'd run factorial combination trials and map each compound's binding target.
- **Cardiovascular and metabolic disease are the most preventable of the big four; cancer is the most inevitable.**
  Cancer requires accumulated mutations plus immune decline, so it may respond least to longevity interventions. Dementia is likely modifiable, but the data are thin. Kennedy criticises Alzheimer's research for spending 30 years on plaque and imagines an epitaph: 'cleared plaques, died of Alzheimer's at 94.'

EXAMPLES

- **Yeast deletion screen with Matt Kaeberlein**
  Of about 5,000 yeast genes, roughly 300 deletions extended lifespan, pointing to mTOR and protein translation. The paper had about 80 authors.
- **Time-release alpha-ketoglutarate (Rejuvant; Kennedy sits on the company's board)**
  In mice: 5–10% longer life and a large drop in frailty, with added benefit from vitamin A in males and vitamin D in both sexes. A placebo-controlled six-month human trial, about US$1–1.5 million, finished but isn't analysed. An earlier uncontrolled methylation study claimed a few years of 'reversal.'
- **Urolithin A and spermidine**
  Urolithin A cut frailty in male but not female mice; it's being repeated, and Kennedy's lab found unpublished binding targets. Spermidine reversed high-fat-diet metabolic dysfunction in old mice and extended lifespan in his hands.
- **Kennedy's n=1 sublingual NAD effect**

100 mg sublingual NAD with apigenin (a CD38 inhibitor) plus AKG: he could run at 150–155 bpm with less breathlessness and once ran 12 km instead of 5. He stresses it's anecdotal. He notices nothing from NR or NMN and doubts they raise NAD much.

• Rapamycin timing

Kennedy has poor runs within 24 hours of a dose and good training 3–4 days later. Attia plans to test shifting his own dosing day.

OTHER RELEVANT

• Expect healthspan, not immortality

Attia tells patients the realistic gain is 7–10 extra years of far better life. Kennedy's grandmother bowled a 238 at 93 and lived to 101—a 20-year phase shift, not escape from decline.

• Skip commercial epigenetic age tests

Their reliability is poor; standard labs managed aggressively are more informative and actionable.

• Vet longevity clinics for safety and honesty

Kennedy wouldn't pay ~$100,000 for follistatin gene therapy. He's tried IV MSCs and is cautious with growth hormone. He's seen infections from offshore treatments, and judges providers on transparency about data and safety.

• Don't forget proven basics

Kennedy finds HRT use remarkably low worldwide and thinks most women should be asked why not, rather than whether. Protect lean mass—his biggest worry with GLP-1 drugs—and do resistance training, as he started doing.

355 – Skincare strategies, the science of facial aging, and cosmetic-intervention guidance

Guest: Dr. Tanuj Nakra & Dr. Suzan Obagi
Date: 2025-06-30 · Duration: 3:10:33
URL: https://www.youtube.com/watch?v=9iHxTvG1_3k

KEYPOINTS

• Facial aging means losing scaffolding: bone, fat pads and skin.

Oculofacial plastic surgeon Tanuj Nakra and dermatologic cosmetic surgeon Suzan Obagi describe about 11 plump fat compartments on each side of a young face, most of which shrink with age. CT studies following the same people over 15–20 years (Rohrich and Pessa) show the eye sockets widening and the cheekbones, maxilla and mandible receding. Retaining ligaments that tether skin to bone then show up as tear troughs and folds. Nakra frames it as four changes: skin, volume, gravity and bone.

• Women's faces age about 20 years faster than men's between 50 and 60–70, largely because of hormones.

Obagi says facial bone loss mirrors the post-menopausal drop in hip bone density. As the mandible recedes the neck loosens, which is why 50-year-old women often say 'I hate my neck'. She argues for discussing hormone replacement early in menopause. Weight cycling also thins the face: each pregnancy's gain and loss comes off the face and doesn't return there.

• Facial fat behaves differently from body fat, and chronic stress may speed up its loss.

Why facial fat shrinks while body fat grows isn't understood. Fat pads even differ in color within the eyelid, partly from beta-carotene. Nakra sees peak-stress decades (30s–40s) accelerating facial volume loss and changes in collagen and elastin, and Peter suggests cortisol may break down facial fat even as it builds body fat. Fat grafted from the abdomen keeps behaving like abdominal fat and swells if the patient gains weight.

• Daily sunscreen is the non-negotiable first step. Obagi insists on mineral formulas.

An Australian randomized trial found that four years of daily sunscreen meant fewer lines and wrinkles. UVA ('aging') and UVB ('burning') damage DNA, collagen and elastin, and visible and infrared light add pigment and possibly deeper changes. Obagi prefers zinc oxide or titanium dioxide, citing absorption of avobenzone and oxybenzone into the blood and possible hormone effects. She and Nakra say chemical filters degrade within about an hour in strong sun and that nothing above SPF 50 is meaningful. Those are their clinical views. Darker skin ages more slowly, mainly because melanin forms a 'parasol' over the cell nucleus.

• Retinoids are step two, and the strength should rise with age.

Collagen production peaks around 18. Retinol (over the counter, weakest) converts to retinaldehyde, which converts to retinoic acid (prescription: 0.025/0.05/0.1%, about $80–100 a tube that should last about 3 months). Obagi starts sensitive patients on retinaldehyde five nights a week and tretinoin two, and says skin adapts within 6–8 weeks. Nakra builds up from 2–3 nights a week or mixes in 1% hydrocortisone. Use a fingertip unit including under the eyes, never stop in summer (sensitivity to light fades), and keep it beside your toothbrush.

• Simple routine: gentle cleanser, antioxidant serum, then sunscreen or retinoid.

In the morning: a non-foaming glycerin-based cleanser (body soap strips the face), a vitamin C serum, then sunscreen. At night: cleanser, serum again (Obagi says the day's oxidative load depletes it), then retinoid, applying thinnest to thickest. Vitamin C supports collagen synthesis, acts as an antioxidant and evens pigment, and topical application reaches far higher skin levels than oral doses. It degrades easily, so stabilized formulas are worth paying for, unlike retinoids and sunscreen. Nakra's 'cheapest trick': nightly petroleum jelly visibly thickens and smooths skin within 30 days.

• Treat cystic acne early, because the scars last a lifetime.

Obagi calls cystic acne, which affects perhaps 20% of adolescents, a dermatologic emergency because of scarring and psychological harm. She avoids long antibiotic courses because of the gut microbiome and moves quickly to isotretinoin, about 5 months, which clears roughly 85% of people. It requires pregnancy prevention, no alcohol, and checking triglycerides and liver enzymes. She considers the depression scare poorly supported, since depression scores often improve. Photodynamic therapy with ALA and red light is an alternative.

• Obagi's 5 Rs of rejuvenation: relax, refill, resurface, redrape, renew.

Relax overactive muscles with neuromodulators, refill volume with fat or filler, resurface the skin (Obagi says better skin gets noticed before a lift does), redrape with energy devices or a facelift, and renew with ongoing maintenance, mostly through skincare at home. Resurfacing runs from non-ablative options (light peels, IPL/BBL, fractional lasers) to ablative ones (CO2, deep TCA or phenol peels). A full CO2 treatment means 7–10 days in dressings, about 3 weeks of redness, and is done every 5–10 years. Ablative lasers are riskier for darker skin types.

EXAMPLES

• Peter's face as a case study.

Hooded upper lids push his forehead muscle to work constantly (likely enough to qualify for an insurance-covered blepharoplasty), so freezing the forehead with Botox would make him look heavier. His tear-trough hollow could take fat or filler (about $800–1,000 a syringe). The suggested definitive fix is a transposition lower blepharoplasty that moves the eye-bag fat into the hollow, plus resurfacing. Under-eye dark circles have four causes: visible muscle, shadowing, hemosiderin and pigment. He had all four.

• Fillers don't simply vanish after a year.

Nakra regularly finds hyaluronic filler injected 8–10 years earlier still stretching ligaments during surgery. Overfilling of lips and cheeks is his biggest concern.

• Fat grafting, step by step.

Obagi harvests about 120 cc (mainly from the flanks, for the stromal tissue), centrifuges it, and adds PRP and 'nanofat' to improve how much survives. Grafted patients seem to age better.

- **Newborns prefer attractive faces.**
  In Judith Langlois's preferential-looking studies, weeks-old infants looked longer at attractive faces. Symmetry, averageness and sexual dimorphism appear across cultures.

OTHER RELEVANT

- **Choose injectors and surgeons carefully.**
  Look for board certification in the specific area, enough volume (for example at least 25 facelifts or rhinoplasties a year), honest personal complication rates and a comprehensive assessment. Filler injected into a vessel near the eyes, nose or temples can cause blindness or stroke, so seek experienced, physician-supervised care.
- **Skip 'preventive' Botox at 18 and tightening devices before about 40–45.**
  Obagi warns that ultrasound and radiofrequency tightening may cause fat atrophy in younger faces.
- **Don't judge your face by one bad photo or a filtered image.**
  Front-facing cameras distort faces, and almost everyone is asymmetric. Nakra says 95–99% of patients haven't noticed their own asymmetry.
- **Be cautious about big decisions during emotional upheaval.**
  Both doctors start with reversible, low-risk steps and sometimes refer to therapy before considering surgery.

342 Aging well: Peter shares strategies for improving longevity with residents at senior living

Date: 2025-03-31 · Duration: 0:45:16
URL: https://www.youtube.com/watch?v=rRZs9xJ0ulo

KEYPOINTS

• Longevity means both lifespan and healthspan, and healthspan has three parts.

Speaking with residents of a senior living community, in a conversation hosted by his daughter Olivia, Peter defines longevity as maximizing how long and how well you live. Healthspan covers the physical (free of pain, able to garden, golf, hike or simply care for yourself), the cognitive (a sharp mind) and the emotional (purpose, happiness, connection). Asked to choose between living to 80 in good health with a quick end, or to 100 with 20 years of painful decline, he expects almost everyone would pick the first.

• It's never too late to start, and the biggest gains go to the least active.

Peter compares it to saving for retirement: earlier is better, but starting late still pays. Trials in older adults show people who first lift weights in their 60s and 70s benefit remarkably. Adding 3 hours a week of exercise barely changes things for someone who already trains, but taking a sedentary person to 3 hours (30 minutes, 6 days a week) has an 'enormous' impact.

• The four horsemen are heart disease, cancer, neurodegeneration and metabolic disease.

Cardiovascular and cerebrovascular disease is the leading cause of death for men and women, in the US and globally. Cancer is close behind and is many different diseases ('prostate and breast cancer are as different as a pickup truck and a Corolla'). Third is dementia, including Alzheimer's and vascular dementia. Fourth is the spectrum from insulin resistance and fatty liver to type 2 diabetes, which rarely kills directly but raises the risk of the other three by about 50%.

• Surviving a heart attack is a second chance to act on the controllable risks.

About half of heart attacks are immediately fatal. Survivors should target what drove the first event: cholesterol, blood pressure and smoking (the big three), plus exercise and metabolic health. Peter knows people who had a heart attack at 60, lost 30 lb, quit smoking, managed their numbers, started exercising and lived into their 90s.

• After 65, falls drive a five- to sixfold rise in accidental death.

At Olivia's age, accidental deaths are mostly car crashes and overdoses. At Peter's, overdoses. Over 65, almost all are falls. Three things drive it: loss of type 2 (fast-twitch) muscle fibers, which shrink from about age 25 and supply the reactive step that catches a stumble; lower muscle mass; and lower bone density. Women are more affected, partly because many didn't receive hormone therapy after menopause and estrogen is the most important hormone for bone. About half of hip-fracture survivors never regain their previous mobility.

• Heavy strength training can rebuild bone, even in frail older women.

Peter's favorite example is Belinda Beck's LIFTMOR trial in Australia. Women over 65 with very low bone density, who had only walked or done yoga, were randomized to supervised heavy training: squats, deadlifts, presses and pull-up progressions. Some ended up deadlifting their own body weight, and scans showed bone density increased, which was once thought impossible. Fast-twitch fibers also respond only to heavy loads plus reactive movement like bouncing, side-to-side steps and jumping rope. 'Lifting weights is something every person on this planet should be doing.'

• Older adults need about 1 g of protein per pound to fight anabolic resistance.

Peter's diet principles: don't eat too much or too little, and find a pattern you can stick to, whether vegetarian, Mediterranean or steak and potatoes. Aging muscles respond less to a given amount of protein (anabolic resistance), so needs rise just as many older people, especially women, eat like 'little birds'. If you weigh 150 lb, aim for about 150 g. Half that is clearly too little. Overweight people can base it on a reasonable goal weight. Track a week in an app to check.

• Sleep in later life: protect the wake time, cut naps, and time fluids, food and alcohol.

With age, sleep gets lighter and nighttime urination more common. Thirst also becomes a less reliable signal, so hydrate during the day but taper fluids before bed. Leave about 3 hours between dinner and bed, minimize alcohol, and keep the room dark and cold. The biggest lever is a fixed wake-up time with no daytime naps, which builds sleep pressure. If you still struggle to fall asleep, try the lowest-dose melatonin (about 300 mcg, no more than 1 mg), which helps start sleep but doesn't keep you asleep. Ashwagandha helps some people.

EXAMPLES

• 'Sitting is to lower back pain what bourbon is to alcoholism.'

Peter argues most people are less fragile than they think and that inactivity often worsens back pain. Bone-on-bone joints may need replacement, which he says has transformed quality of life, and a good physical therapist can sort out what training can fix.

• Klotho.

Neurologist Dena Dubal studies klotho, a brain-protective protein that exercise raises and age lowers (children make about six times more). In mice and monkeys it reverses cognitive decline. Human trials are starting, so a drug is perhaps 7–10 years away in the best case.

• APOE.

Two copies of APOE4 raise Alzheimer's risk about tenfold and one copy about twofold. About 60% of people are 3/3, Peter included, but he acts as if he's high risk. Women face nearly double men's risk.

• A hip fracture followed by decline.

An audience member's mother fell, broke her hip and then declined cognitively. Peter suspects the long physical and mental inactivity sped up decline by years, while noting this is hard to prove.

OTHER RELEVANT

• Start strength training now, with guidance.

Work up to heavy, supervised compound lifts and add balance and reactive drills to protect against falls.

- **Prioritize protein, ideally from dairy, beef and eggs.**
  For supplements, whey, casein or egg protein are best. Many people who can't tolerate dairy react to the sugar (lactose), not the protein.
- **Guard your social network and purpose.**
  Peter calls social support and a sense of purpose perhaps the most important emotional-health tools. He cites the familiar pattern of a long-married spouse dying within a year of the other.
- **If you've had a cardiac event, treat it as a turning point.**
  Work with your doctor on lipids, blood pressure, smoking and exercise.

333 Longevity roundtable—the science of aging, geroprotective molecules, & lifestyle interventions

Guest: Steven Austad, Richard Miller & Matt Kaeberlein
Date: 2025-01-27 · Duration: 2:55:00
URL: https://www.youtube.com/watch?v=NU98SXBCjz4

KEYPOINTS

• Healthspan and lifespan aren't a seesaw when you target aging itself.

Miller, who runs the NIA's Interventions Testing Program (ITP), says every drug that extends mouse lifespan does so by delaying both fatal and non-fatal diseases, much like exercise or avoiding insulin resistance. Austad counters that in humans the gap between healthspan and lifespan is widening fastest in the US and in women, because medicine keeps sick people alive longer. Kaeberlein reconciles the two: slowing aging moves both together, while disease-by-disease care stretches the sick years.

• US life expectancy lags because of deaths in middle age, not old age.

Attia notes the US spends about 80% more than peer countries yet ranks lowest among OECD nations. That's because of maternal and infant deaths, overdoses, guns and suicide. Past about 65, Americans jump to the top, reflecting 'medicine 2.0' extending life with chronic disease. With 60% of Americans having a chronic disease, many spend decades in 'sickspan.'

• Aging research gets a sliver of funding despite driving nearly every leading killer.

Nine of the top 10 US causes of death have aging as their biggest risk factor. Yet biology-of-aging research gets about 0.5% of the NIH budget (about $350 million). Disease lobbies guard their turf: when NIA council members floated diverting a few percent of Alzheimer's money, appropriations staff called the next day. Miller's talks showing anti-aging drugs cut age-adjusted cancer in mice tenfold draw no follow-up from cancer centres.

• Calling aging a disease is the wrong framing.

Miller calls it a 'fundamental error' because aging is a risk factor for diseases. Austad says the label is a marketing ploy for funding. Kaeberlein says the FDA doesn't require it—Austad's TAME team got metformin trial interest by framing the endpoint as multimorbidity. Austad estimates privately funded aging research now outspends public money at least 2:1.

• Consumer epigenetic age tests aren't reliable.

Kaeberlein sent duplicate samples from one day to four companies. At age 53.7, results ranged from 42 to 63; one company's duplicates were 20 years apart. Biological aging is real—dogs age about seven times faster, and single genes like daf-2 shift the rate—but Miller and Attia say no single number beats a rich clinical picture. Life insurers don't use the tests.

• The 'hallmarks of aging' both helped and harmed the field.

Miller says the list became 'biblically sacrosanct,' letting grant writers skip proving causation and starving ideas off the list. Kaeberlein agrees it narrowed the field prematurely—we may understand 'about 0.005%' of aging—but says it gave the field mechanistic credibility. Austad notes reviewers punish 'fishing expeditions' and breakthrough ideas.

• Speed-type aging-rate indicators could make human trials feasible.

Biomarkers are like an odometer and change only by old age. Miller's lab found about 12 markers that shift early in every slow-aging mouse model, across drugs, caloric restriction and five gene mutants. Examples include fat macrophage shifts, UCP1, and the enzyme GPLD1, which exercise also raises and which boosts neurogenesis in mice. A new grant tests whether they stay unchanged with ineffective drugs. Austad warns that mouse findings may not carry over to humans.

• Senescent cells are hotly disputed.

Miller argues the concept grew from Hayflick taking a lunchtime joke seriously, and that 'senescent cell' and 'SASP' lump unrelated phenomena together. The ITP found fisetin had no lifespan effect and no change on six senescence markers. His group went 0 for 7 replicating senescent-cell clearance in the Mayo genetic model. Austad and Kaeberlein point to evidence that clearing p16-positive cells improves health, and to NIH's roughly $600 million senescence network.

• Rapamycin works as cancer prevention even where it fails as chemotherapy.

Kaeberlein: established tumours evolve around the mTOR brake, so disease-stage biology differs from aging biology. ITP rapamycin is mixed into food daily. Weekly human dosing of about 3–10 mg traces to Joan Mannick's everolimus vaccine trials, where 5 mg weekly worked best. The idea that side effects come from mTORC2 is less proven than assumed. Partridge's lab found a MEK/ERK inhibitor adds to rapamycin through a separate pathway.

EXAMPLES

• Resveratrol's coconut-oil mice

The 'first drug to extend mouse lifespan' worked only in mice on a 60% coconut-oil diet. Their fatty livers were compressing their lungs, as a later paper quietly noted. Nobody at the table defends resveratrol for aging.

• NAD precursors

The ITP's negative result is the strongest evidence. Oral NR and NMN appear to be broken down to nicotinamide in the gut. One mouse study found kidney inflammation from NMN in aged mice, which Kaeberlein flags given NMN sold for pets.

• Metformin

Miller co-wrote a review arguing that the famous Bannister diabetic-survival study is methodologically flawed; metformin didn't extend ITP mouse lifespan. Austad finds the observational signals worth a trial, and TAME has finally begun enrolling on a small budget.

• Canagliflozin and GLP-1 drugs

The SGLT2 inhibitor canagliflozin extended male mouse lifespan, mechanism unclear. GLP-1 drugs await an easy oral form for ITP testing; oral semaglutide requires laborious fasting protocols.

• Parabiosis and plasma exchange

Austad and Kaeberlein are cautiously optimistic, since plasma exchange is existing technology. Miller wants the specific harmful or helpful factors identified rather than 'medieval' mixtures. Parabiosis surgery itself shortens rodent lifespan, a possible

confounder.

OTHER RELEVANT

- **Define your own healthspan**
  Austad says health means being able to do what you love. Attia's 'marginal decade' exercise covers physical, cognitive, emotional and social goals.
- **Immune aging matters**
  Attia would add immune decline as a fifth 'horseman.' Young patients survive pneumonias that would kill a 75-year-old, and flu or pneumonia remains a top-10 cause of death.
- **Be sceptical of longevity products**
  Miller blames a profitable industry selling untested products 'with a wink and a nod and a lawyer.' Kaeberlein urges caution about stacking supplements without evidence.
- **The economics are enormous**
  Austad cites an analysis by economist Andrew Scott valuing one extra year of healthy life at about $38 trillion.

311 Longevity 101: a foundational guide to Peter's frameworks for longevity

Date: 2024-07-29 · Duration: 1:30:02
URL: https://www.youtube.com/watch?v=B94rbrZkXPI

KEYPOINTS

• Longevity has two parts: lifespan and healthspan

Peter describes longevity as a function of two vectors. Lifespan is binary and objective: you are either alive or dead. Healthspan is analog and subjective, with physical, cognitive and emotional parts. His working goal is to live years or a decade longer, not double lifespan, and to slow the decline of healthspan. Someone who wants to reach 95 presumably wants to function like a healthy 75-year-old at the end, not suffer like Tithonus, who was granted immortality without eternal youth.

• Physical and cognitive health decline with age, but emotional health doesn't have to

Peter says he is clearly past his physical and mental prime, but he has gained in some areas: he moves more intelligently, and his intelligence has shifted from fluid toward crystallized. Emotional health roughly follows a shallow U-shaped curve with a dip around the late 40s. That means it can keep improving: he says he is better off emotionally than a decade ago and expects to be better still in another decade, provided he does the work.

• About three-quarters of the lifespan gain comes from pursuing health

Peter's 'bold', untested belief is that if you only pursued strength, endurance, balance, processing speed, emotional health and relationships, and never thought about heart disease, cancer or Alzheimer's, you would get about three-quarters of the way to an optimized lifespan. Healthspan work is a 'two-fer': it pays off on its own and very likely extends life more than the disease-specific efforts of conventional medicine.

• Medicine 3.0 adds to Medicine 2.0 rather than replacing it

Medicine 1.0 relied on gods, spirits and humors, and life expectancy was in the late 30s to early 40s. Francis Bacon's scientific method, the microscope, germ theory, sanitation and antibiotics roughly doubled lifespan in about 100 years, and RCTs then supercharged this Medicine 2.0. But lifespan has stalled against chronic disease. Medicine 3.0 prevents disease early and aggressively, tailors care to the individual, and gives healthspan equal weight. Peter illustrates the split: of 100 units of health spending, perhaps only 60 are needed, split 30/30.

• Atherosclerotic disease is the most preventable of the Four Horsemen

Atherosclerotic disease needs three things: apoB-carrying lipoproteins entering the artery wall, endothelial damage, and inflammation after those particles oxidize. Peter says genetics and environment drive it with little role for chance. RCTs, Mendelian randomization and epidemiology all show a log-linear drop in risk as apoB falls. Smoking, blood pressure and insulin-resistance markers (glucose, insulin, homocysteine, uric acid) weaken the endothelium. About 50% of first heart attacks are fatal, and he calls the roughly 19 million deaths a year a 'bizarre tragedy' given the tools available.

• Cancer has fewer known levers and depends partly on chance

Clear genetic drivers exist (BRCA1/2, Lynch syndrome), but most family risk is polygenic and unidentified. Smoking and obesity are the clear environmental triggers, and about two-thirds of cancers are strongly tied to obesity. He thinks growth factors such as insulin and IGF matter more than the fat itself. At equal calories, evidence that specific foods such as red meat or soy cause cancer is 'scant'. Much of the rest may be bad luck from acquired mutations (Vogelstein). Metastatic solid tumors have about the same 10-year survival as 50 years ago, which is why he favors early, aggressive screening.

• For dementia, prevention comes first, second and third

'What's good for the heart is good for the brain': every measure that lowers atherosclerotic risk (lower apoB and blood pressure, better metabolic health, not smoking) also lowers dementia risk. Exercise has an even larger and more certain effect on neurodegeneration. With almost no effective treatments, building cognitive and movement reserve is the main defense. Metabolic disease, driven mainly by overnutrition and insulin resistance, adds roughly 25–50% to the risk of the other three Horsemen.

• Two nutrition claims are highly certain: energy balance and protein

Peter admits he spoke with unwarranted certainty about nutrition 12 years ago. He is now confident of only two things. Total energy intake matters most, though quality and processing still count (1,000 calories of Tic Tacs isn't broccoli). Protein is the macronutrient not to compromise on: about 1.6 g/kg/day as a default, perhaps 1.2 or even 1.0 g/kg with high-quality protein in less active people, and more with age because of anabolic resistance. To eat less, you can restrict calories, restrict foods or restrict eating windows.

• Exercise has the biggest single effect

Exercise beats every other tool for both lifespan and healthspan, with the possible exception of emotional health when it is severely broken. Training for the Centenarian Decathlon has four parts: stability (bracing, rib position, foot mechanics, controlled force), strength and power, aerobic efficiency (all-day pace, fat oxidation), and VO2 max (engine size). You set late-life goals, work out what each requires (for example a VO2 max of about 31 mL/kg/min), and work backward to today's training to allow for decline.

• Every supplement should pass a set of questions

Is it meant to extend lifespan or improve healthspan? If lifespan, does it target a specific disease or aging broadly? If healthspan, does it help cognition, physical performance or emotional health? Are there human or relevant animal data on safety and efficacy? How is purity verified? He treats drugs as tools: refusing all of them is like telling a contractor not to use a hammer.

EXAMPLES

• The funeral that started the Decathlon

At a 2018 funeral for his best friend's mother, who died at about 89, Peter realized she had lost golf, gardening and playing with her grandkids a decade earlier and later developed dementia. He had trained without purpose since quitting competitive cycling at the end of 2014, and resolved to train for the last decade of his life instead.

• Specific goals versus the Decathlon

His wife's Boston Marathon training, or a jiu-jitsu tournament in six months, needs specific training. Most people have no such

event, so he says the Centenarian Decathlon is the best default framework he knows.

- **Late starters**
  He writes about people who started committing to their health in their 70s and in their 80s are doing better than in their 60s. He compares it to braking before a red light: earlier is easier, but it's rarely too late.
- **Three first-visit questions**
  Using a DEXA scan and blood work, Peter checks whether a patient is over- or undernourished, adequately muscled, and metabolically healthy. He estimates about 70% of people are overnourished.

OTHER RELEVANT

- **A short list of sleep basics**
  Keep consistent bed and wake times, allow about 8 hours in bed, keep the room dark and cold, avoid work, social media and upsetting stimuli for 2 hours before bed, and stop food and alcohol 3 hours before. He estimates 80 of 100 poor sleepers would improve.
- **Treat emotional health as foundational**
  Even if misery somehow added years, few would choose it. Peter calls this pillar possibly the most important, because without it the others don't matter, and says your mental 'software' can be modified.
- **Start with one pillar**
  If you feel overwhelmed, pick the area where you're most likely to succeed, such as sleep, and change nothing else. Early success makes the other changes easier and builds a sense of control.

300-Special episode: Peter on exercise, fasting, nutrition, stem cells, geroprotective drugs, & more

Date: 2024-05-06 · Duration: 1:48:22
URL: https://www.youtube.com/watch?v=Io5xV9rtbm4

KEYPOINTS

• Peter sorts claims into five evidence tiers: proven, promising, fuzzy, noise and nonsense.

For the 300th episode, Nick Stenson put listener-submitted topics, drawn from a few thousand Instagram comments, to Peter for ranking. In biology nothing is truly proven, so 'proven' means the chance it's untrue is so small it would be foolish not to act. 'Promising' has strong data with a missing piece, such as human or randomized trial evidence. 'Fuzzy' has inconsistent or contradictory data. 'Noise' has data too thin to judge, perhaps with an appealing mechanism. 'Nonsense' has been studied and found to be bunk. Peter stresses that rankings move as evidence changes.

• Rapamycin: promising, not proven.

Rapamycin was discovered in Easter Island soil bacteria in the 1960s and championed by Suren Sehgal. The FDA approved it for organ transplantation in 1999. In 2009 the Interventions Testing Program (ITP) showed it extended life in male and female genetically diverse mice, even when started late in life, which no other drug had done. It also works in yeast, worms and flies. What's missing is human evidence that intermittent dosing, which short trials suggest can enhance rather than suppress immunity, actually extends life. Peter has taken it for about six years, yet fewer than 10% of his patients do, and he calls handing it out 'like Tic Tacs' irresponsible.

• Metformin: downgraded from promising to fuzzy.

Bannister et al. (2014, UK data) found diabetics on metformin had about 15% lower all-cause mortality than non-diabetics, despite worse glucose control. Peter argues this was likely driven by informative censoring, since patients were dropped when their medication changed, which selected for the healthiest. Keyes et al. (2022), using Danish data that included twins discordant for diabetes, found metformin users still had 33–80% higher mortality. Metformin also failed in the ITP except when combined with rapamycin. The TAME trial may eventually test it in humans.

• NAD and its precursors: noise. Resveratrol: nonsense.

NAD declines with age and is needed by sirtuins, but whether the decline is causal is unknown. The best human data are tiny: a four-month ALS study of nicotinamide riboside (NR) plus pterostilbene showing slowed functional decline, a 20-person Parkinson's study confounded by levodopa timing, and a small MCI study with no cognitive benefit. Peter takes no NR, NMN or infusions. Resveratrol's 2006 mouse benefit came in mice fed 60% coconut oil whose fatty livers collapsed their lungs. The rigorous ITP test at 300 ppm in food, versus under 2 ppm in wine, showed nothing, a result proponents signed off on at the time.

• VO2 max, muscle mass and strength are as close to proven as it gets.

Peter ranks them alongside quitting smoking and controlling blood pressure. Fitness predicts lifespan better than cholesterol, blood pressure, glucose or even smoking, partly because 'you can't cram for the test': a top-2–3% VO2 max or strong grip reflects years of work. He tells patients chasing supplements that they're 'picking up pennies in front of a steam train.' Even if exercise were lifespan-neutral, he says, its quality-of-life benefits would make it worth it.

• Long-term fasting: fuzzy, and Peter stopped his own protocol.

Caloric restriction, like rapamycin, extends life across model organisms. But the duration, depth and frequency that might work in humans are untested, and he admits his old routine of 7–10 days of water-only fasting each quarter plus 3-day fasts in other months was 'made up.' Fasting crashed his thyroid and androgen markers, and over about three years he lost roughly 16–20 lb of muscle he couldn't regain. In about 2021 he stopped, partly also to avoid fasting in front of his kids. He still uses time-restricted eating for calorie control.

• Energy balance: between promising and proven.

A study funded by an organization Peter once ran found that equal-calorie diets with very different macronutrients don't meaningfully change energy expenditure. Thermic effects and appetite differ by food, but someone switching from 3,000 balanced calories to 3,000 keto calories who rapidly loses weight is, he believes, moving more or eating less than they realize. Changing your mind with new data is what separates a scientist from an advocate.

• 'Red meat causes cancer' is nonsense in Peter's ranking, though diet patterns matter.

In a European cohort of nearly half a million people, the heaviest red and processed meat eaters (about 160 g/day) versus near-zero eaters (about 20 g/day) had colorectal cancer risks of about 1.7% versus 1.33%. That's about 0.4 percentage points, or treating roughly 250 people to prevent one case, even assuming causation. Peter blames food-frequency questionnaires and healthy-user bias, and suspects low fiber and vegetable intake drive much of the risk. He considers the weak hazard ratios incompatible with Bradford Hill causality, unlike smoking.

EXAMPLES

• Blood flow restriction (BFR): promising.

Partially restricting venous return with a cuff during light, high-rep lifting produces clearly larger strength and size gains than the same work without a cuff. Jeremy Loenneke's meta-analysis showed this, and each limb can serve as its own control. BFR hasn't been compared head-to-head with heavy lifting. Peter used it after shoulder surgery, uses it for finishers, and has post-op knee patients do bodyweight leg extensions with a cuff.

• Stem cells for osteoarthritis: between noise and fuzzy.

Dog studies are mixed, cell types and protocols vary, and the FDA doesn't authorize them, making the field 'the Wild West.' Still, Peter would try an injection for a borderline rotator-cuff tear before surgery.

• 'Sugar is poison' is the wrong question.

As with Tylenol or alcohol, the dose makes the poison. In a nine-month calorie-controlled mouse study discussed with Rick Johnson, fructose didn't change body weight. Liquid sugar does drive overeating. As a teen training six hours a day, Peter drank two liters of orange juice as a snack at about 4% body fat.

- **Sugar substitutes.**
  Cancer scares came from rats fed the equivalent of about 800 diet sodas a day (saccharin) or about 20 (aspartame). Saccharin, aspartame and sucralose look mildly negative metabolically. Stevia, erythritol, xylitol and allulose look better. Peter chews xylitol gum for tooth enamel.

OTHER RELEVANT

- **Master the basics before supplements.**
  Build VO2 max, muscle mass and strength first. Geroprotective pills don't substitute for them.
- **Swap diet soda for water, not regular soda.**
  Peter's advice to people struggling with weight or glucose who drink a lot of artificially sweetened drinks.
- **Fatty liver.**
  Weight loss improves it regardless of diet. Peter still advises such patients to avoid alcohol and limit fructose to modest amounts of fruit, while admitting the trial evidence is incomplete.
- **Use a three-question nutrition triage.**
  Are you over- or under-nourished? Adequately muscled? Metabolically healthy? The answers guide how you eat and train.

281 Longevity drugs, aging biomarkers, and updated findings from the Interventions Testing Program

Guest: Richard Miller
Date: 2023-12-04 · Duration: 2:31:20
URL: https://www.youtube.com/watch?v=sZ-krUa6VH0

KEYPOINTS

• The ITP is a small, rigorous program for testing longevity drugs in mice.

Miller, who directs aging research at the University of Michigan, describes the NIA-funded Interventions Testing Program. It runs at three sites: Michigan, UT San Antonio (Randy Strong) and the Jackson Laboratory. Each gets about $1 million a year in direct costs, roughly $4.5 million in total. Anyone can nominate a compound; there were 28 nominations in a record year, and about six are chosen annually. About 100 drugs have been tested in 20 years. Miller says the budget is not too small.

• Genetically diverse mice are essential; the standard inbred B6 mouse misleads.

About 97% of aged-mouse requests are for one inbred strain, C57BL/6. Every B6 mouse is identical and inbred, many are deaf by a year old, and drug effects often don't carry over to other strains. Miller compares it to testing a cancer drug on identical triplets. The ITP uses UM-HET3 mice, which share four grandparent strains, so the population is reproducible but every animal is different. About 12,000 DNA samples from mice with known lifespans have also allowed lifespan genes to be mapped.

• Study design is pre-specified and statistically conservative.

The primary endpoint is overall death risk, roughly equivalent to median lifespan. For maximum lifespan they use the Wang–Allison test: what share of the mice still alive at the pooled 90th percentile were treated? Each year has 300 male and 300 female controls and 150 of each sex per drug. That gives 80% power to detect about a 12% effect even if one site failed. Michigan males consistently live 5–10% longer than at other sites, for unknown reasons, so results are analysed site by site and then pooled. Drug levels in food and tissue are confirmed first. Rapamycin needed encapsulation because stomach acid destroyed about 90% of it.

• Four drugs give more than a 10% lifespan gain, compared with about 3% for curing cancer.

Work by Jay Olshansky and Bruce Carnes (1990) estimated that eliminating cancer or heart attacks after 50 would raise human median lifespan less than 3%. The ITP's winners are rapamycin, acarbose, 17; ÖW7G adiol and canagliflozin. Rapamycin plus acarbose gave a 29% increase in males, the largest yet and the first gain from a combination. Rapamycin consistently benefits females more, possibly because their blood levels are about three times higher. Canagliflozin works only in males, and in aging females blood levels reach about 10 times those of young males, likely toxic.

• Starting late still works.

Rapamycin started at 20 months (roughly a 55–60-year-old human) extended lifespan as much as starting young, in both sexes. 17; ÖW7G adiol and canagliflozin work in middle-aged males. Acarbose works about half as well when started late. Mice given acarbose or 17; ÖW7G adiol in middle age also had better grip strength and rotarod performance. Rapamycin, originally nominated by Dave Sharp based on mTOR genetics in worms and flies, also boosted vaccine responses in old mice.

• 17; ÖW7G& F–öÂ —2 Ö ÆRÖöæÀy puzzle.

It's a stereoisomer that barely binds classic estrogen receptors. The original idea was to give males estrogen's benefits without feminization. But males ended up outliving females, and females gain nothing. Treated males produced over 20-fold more estriol, but only if not castrated. In unpublished data, 16-hydroxyestriol seems to work in males at least as well, but it's the first drug found to shorten female lifespan.

• 'Aging rate indicators' act like a speedometer rather than an odometer.

Miller doesn't think we have good biomarkers of biological age. Instead, his lab found 13 traits that shift the same way in 10 slow-aging mouse models (four mutants, calorie restriction, four drugs and a PTEN overexpressor), even in young adults. Examples include more UCP1 in all three fat depots, fewer inflammatory M1 and more M2 macrophages in fat, higher BDNF and doublecortin in the brain, more of the muscle protein FNDC5 and blood irisin, and higher GPLD1 (an exercise-linked factor tied to cognition). For the male-only drugs, these changes appear only in males. Ames dwarf mice given growth hormone for just six weeks as babies lost both their long life and these traits permanently.

• RNA levels predict protein changes poorly.

Gary Churchill's Jackson Lab work found only about 30% of age-related protein changes matched mRNA changes. GPLD1 is regulated by cap-independent translation, not transcription. Selective protein breakdown (chaperone-mediated autophagy) also shapes the proteome. Miller says transcript-only studies are 'not only incomplete but mostly wrong.'

• Notable failures: resveratrol, metformin, nicotinamide riboside and fisetin.

The NIA director required them to test resveratrol, and it failed at doses David Sinclair recommended. Miller says the positive study used mice on a 60% coconut-oil diet, and experts' suggested doses spanned a million-fold range. Metformin failed, and others confirmed it. NR failed alone but will be tried in combination, and Miller keeps an open mind about NAD. Fisetin, suggested by Jim Kirkland and Paul Robbins, didn't extend life and didn't reduce p16, p21 or ;"Öv Â Ö kers in blinded tissue analyses.

EXAMPLES

• Over-the-counter winners

In a paper under review, the seasickness drug meclizine (found by screening for mTOR inhibitors) and astaxanthin (what makes farmed salmon pink) each extended male lifespan by about 10%. Neither changed maximum lifespan. They're the first ITP winners you can buy without a prescription; higher doses are being tested.

• Captopril

The blood-pressure drug gave a small lifespan gain, which surprised Miller since mice don't die of hypertension. It's being retested at a higher dose.

• Senescence skepticism

In the original ;"Öv Â 6¶–â 7GVG•, the highest score was about 1 positive cell in 10,000, in a woman in her 90s. Miller argues 'senescent cell' lumps distinct cell types together, like asking whether you 'believe in stress.'

• Euthanasia method

Rapid CO2 makes mice unconscious in 5 seconds. The newer gradual method takes about 7 minutes, doubles glucose and floods the body with adrenaline, which would distort measurements.

OTHER RELEVANT

• Sex differences in drug metabolism

Liver drug-metabolizing enzymes differ greatly by sex in mice and humans, yet human dosing rarely accounts for it. Attia calls this a missed opportunity.

• Bridging to humans

Miller is testing aging rate indicators in muscle and fat biopsies from people in their 70s in a UCSF study, and searching for blood metabolites that mirror tissue levels.

• Cognition next

A new Michigan neuroscientist will test whether lifespan drugs also preserve memory.

• Tissue sharing

Frozen tissues from 22-month-old mice have gone to outside labs, though NIA is moving to slower, once-a-year allocation. Philanthropists could fund additional ITP work through the universities.

276 Special episode: Peter on longevity, supplements, protein, fasting, apoB, statins, & more

Date: 2023-10-23 · Duration: 1:24:16
URL: https://www.youtube.com/watch?v=em5xwtivnkg

KEYPOINTS

• Peter doubts anyone alive today will reach 120–150.

In this listener-question AMA with Nick Stenson, Peter says he has seen no evidence we can reverse the underlying processes of aging: mitochondrial dysfunction, protein misfolding, DNA damage and repair, or nutrient-sensing breakdown. He calls the gap between the actual science and the hype in media, social media and podcasts enormous, and dismisses aging clocks claiming a 60-year-old is 'really 35.' For a 50-year-old to live another 70 years, a cure for aging would have to arrive within about a dozen years. Assuming today's tools are roughly as good as it gets, he argues, should make you more serious about using them.

• The realistic prize is one to two extra decades and a stronger 'marginal decade.'

Peter believes his approach can add perhaps a decade to two of life. Heart disease is the one horseman he sees a clear path to nearly eliminating, through 'ultra-primary prevention' from your 30s: apoB never above 30–40 mg/dL, not even a year of mild hypertension, and constant metabolic health. Cancer, dementia, sarcopenia and arthritis can't be deferred indefinitely. So he fixates on the last decade of life: still able to ruck carrying 10–20 lb, swim half a mile and get out of the pool unaided, and get up off the floor. He sees rapamycin's mTOR inhibition as the most promising incremental drug, partly because it worked even when started late in life in animals.

• Geroprotective drugs lack biomarkers, so you can't tell if they're working.

With an ACE inhibitor like lisinopril, blood pressure dropping from 135/85 to 115/75 without dizziness tells you the dose is right. Diet, exercise and sleep all have feedback signals. Drugs aimed at aging itself have none, so you can't know if you're taking too little or too much short of side effects. Peter calls diagnostics an 'unsexy,' underfunded but crucial field. His old fasting routine of 7–10 water-only days each quarter plus 3-day fasts monthly probably cost him about 20 lb of muscle over six years, and he still doesn't know whether it did any good.

• His supplement list comes with a warning: don't copy it.

Mornings: Carlson high-EPA fish oil (about 2 g EPA and 1.5 g DHA), dosed to a red-cell omega-3 level of about 12%. Vitamin D, 5,000 IU, which he calls 'picking up a five-dollar bill in front of a tricycle,' since he considers vitamin D trials poorly done. About 1 g of magnesium total from Slow-Mag, magnesium L-threonate (Magtein) and magnesium oxide. Methylfolate and methyl-B12 (Jarrow) to keep homocysteine below 9. B6 cut from 50 mg daily to three times a week because excess can cause neuropathy. A baby aspirin, which he admits is a 'soft call' with weak evidence. Nights: 600 mg ashwagandha (Solgar), 2 g glycine (Thorne) and Magtein. Phosphatidylserine, about 400 mg, for jet lag. Also AG1, in which he discloses he is an investor and adviser, and Pendulum's probiotic, which he's testing on himself after its small 90-day trial showing a 0.6-point A1C drop.

• Lowering apoB to 30–40 mg/dL takes drugs. Exercise doesn't move it.

Diet has two levers. Cutting carbohydrates lowers triglycerides, and with them apoB. Cutting saturated fat leads the liver to add LDL receptors and pull more LDL from the blood. Few people reach Peter's target that way. His own baseline apoB is about 90–100 mg/dL, roughly the 50th percentile. He takes Repatha (a PCSK9 inhibitor) plus Nexlizet. Its bempedoic acid component is a prodrug activated only in the liver, so it blocks cholesterol synthesis there alone. Ezetimibe blocks reabsorption of cholesterol from the gut and is the weakest of the three. He has no side effects on this combination.

• There's rarely a reason for mega-dose statins now.

Statin efficacy flattens quickly: rosuvastatin delivers about 85% of its maximum apoB reduction at 5 mg, though doses go up to 40 mg. Statins have real, measurable side effects: muscle aches, elevated liver enzymes and insulin resistance. When cost rules out newer drugs, Peter suggests trying low-dose pitavastatin or rosuvastatin to find the best-tolerated option. PCSK9 prices have fallen by more than half, and a twice-yearly injection with a different mechanism is adding price pressure.

• Energy balance matters most in diet, and sustainability beats perfection.

Any diet (keto, paleo, Mediterranean, vegan) eaten in excess pushes fat into the liver and viscera. In Peter's clinical experience, people with profound insulin resistance do best cutting carbs to create a deficit. A 7-out-of-10 diet you can keep forever beats a perfect one you'll abandon in three months. Long-lived populations eat very different diets, and Okinawans' advantage fades as they Westernize, which suggests factors like activity, sleep, stress and social ties matter too. Nutrition science is hard because the organism and the intervention are both complex. Long controlled studies, like the Wisconsin and NIA monkey trials, take decades.

• Protein targets depend on muscle mass and life stage.

An over-nourished but well-muscled person in a calorie deficit can relax to about 0.6–0.7 g per lb. An over-nourished, under-muscled person needs to keep protein high to build muscle while losing fat. Peter isn't convinced by data linking high protein to mortality under 50, which he attributes to excess calories, confounding and very low absolute risk. Under 50 is the time to build muscle, because after 50 'you're clawing on for dear life.' He targets 150–180 g a day over about four sittings, partly from venison jerky sticks of about 10 g each. He discloses an investment in Maui Nui.

EXAMPLES

• The risk-reward grid.

Peter rates interventions as picking up a penny or a gold coin, in front of a tricycle or a train. He recalls teenage games of laying coins on train tracks, and a friend's younger brother who was killed playing chicken with a Toronto subway, the extreme of high risk for no reward.

• 'Good' and 'bad' cholesterol.

Cholesterol is one molecule. LDL and HDL are carriers, and lab panels measure LDL-C and HDL-C. LDL is harmful because it carries cholesterol into the artery wall.

• A biggest glucose spike.

Peter's highest CGM reading, about 180 mg/dL, came after dessert at a carb-heavy vegan restaurant in New York. With CGMs he prioritizes average glucose (a proxy for A1C), then variability, then spikes.

- **Testing a readiness app.**
  For six months Peter compared Morpheus's predicted zone 2 heart rate with his perceived exertion and end-of-ride lactate, and found it tracked well.

OTHER RELEVANT

- **Lp(a) therapy may be coming.**
  An antisense drug eliminated Lp(a) in phase 2. Its phase 3 trial in people who have already had cardiac events will determine approval.
- **A cuffless blood pressure monitor.**
  A wrist device approved in Europe gives about 12 readings a day, and Peter hopes the FDA approves it.
- **Why he stopped long fasts.**
  He no longer travels, the fasts were hard to do at home, and their benefit is unproven.
- **He hopes for continuous lactate sensors.**
  They would make zone 2 and VO2 max training far easier to calibrate.

272 Rapamycin: potential longevity benefits, surge in popularity, unanswered questions, and more

Guest: David Sabatini & Matt Kaeberlein
Date: 2023-09-25 · Duration: 3:01:29
URL: https://www.youtube.com/watch?v=O67pvKxio10

KEYPOINTS

• mTOR connects nutrient availability to whether the body builds up or breaks down.

Sabatini purified mTOR as a student in Solomon Snyder's lab. He describes it as the protein that links nutrients to anabolic versus catabolic states, which is why it touches nearly everything. Rapamycin was found in an Easter Island (Rapa Nui) soil sample collected around 1966–67, and Suren Sehgal championed it. FDA approval for transplant patients didn't come until 1999. Both guests think that transplant history, where the drug was given daily alongside prednisone and other harsh immunosuppressants, gave it an undeserved reputation as a dangerous drug.

• Rapamycin is the most reproducible longevity drug across species.

Kaeberlein found mTOR by accident in an unbiased yeast lifespan screen. Rapamycin, and genetic inhibition of mTOR, extend lifespan in yeast, worms, flies and mice, and appear to improve nearly every healthspan measure tested. His 2007 work with Brian Kennedy and Daniel Promislow showed that genes controlling longevity are often shared between yeast and worms. That's why simple organisms can tell us about aging in mammals.

• How rapamycin works: it's a 'molecular glue,' and it inhibits only part of mTOR's activity.

Rapamycin binds FKBP12 and attaches it to mTOR complex 1 near its active site, like a boulder partly blocking a cave entrance. Some substrates get through and others don't. With prolonged exposure, it also prevents mTOR complex 2 from forming, by binding mTOR before Rictor can join it. Sabatini's postdoc showed this around 2004–2005, and Sabatini didn't believe it at first. Cells need only about 10–15% of complex 2 to keep AKT working. Catalytic (ATP-competitive) inhibitors block both complexes fully. Sabatini says they're highly toxic and can kill a mouse within hours.

• Leucine is sensed by sestrin, at the lysosome.

Tim Peterson's experiments showed mTOR moves onto lysosomes within minutes of adding amino acids, docking on a 'pier' made of about 20 proteins. Earlier work by Joe Avruch had pointed to leucine and arginine as the key signals. Sabatini's lab identified sestrin as the leucine sensor, and its crystal structure shows a small pocket with a lid that fits only leucine. That explains why better-than-leucine mimics have been so hard to make.

• The muscle paradox.

mTOR activation builds muscle, so rapamycin was expected to cause sarcopenia. Instead, rodents treated throughout adulthood kept more muscle into old age, perhaps through reduced inflammation. Kaeberlein notes there's no human data on whether lifespan-type doses blunt resistance-training gains. He also warns that mice are poor models of sarcopenia, so mouse protein-restriction findings may not carry over to people.

• Starting rapamycin in middle age still works.

The 2009 ITP study started treatment at 20 months, about the equivalent of a 60-year-old human, only because the drug couldn't be formulated sooner. Kaeberlein calls it one of the most important studies in the field and says a grant proposing that design would never have been funded. Full dose-response and timing studies have never been done, and his grants for them have been rejected.

• Mannick's everolimus trial changed how the drug is viewed.

In mice, six weeks of rapamycin before vaccination raised flu protection in old animals from about 30% to 100%. In Joan Mannick and Lloyd Klickstein's trial (about 80 per arm), older adults took everolimus for six weeks before a flu shot. Doses of 5 mg weekly and 1 mg daily improved antibody responses, and the 5 mg weekly arm had side effects close to placebo. The guests now call rapamycin an immune modulator rather than an immunosuppressant. A later pivotal trial used RTB101, a non-specific PI3K/mTOR inhibitor, without everolimus. It was stopped early, so it says nothing about rapalogs.

• What people in the off-label survey reported.

Kaeberlein's survey compared about 300 rapamycin users with nearly 200 health-conscious non-users. All data were self-reported. Mouth sores were the only side effect more common in users, at about 15%. Abdominal cramps, depression and anxiety were less common. Most users took 6 mg once weekly, with a smaller cluster at 3 mg and some up to 20 mg. People who took it continuously through COVID reported milder illness and less long COVID, though the numbers were small.

• Why it may work: autophagy, inflammation, or the 'general contractor' effect.

Sabatini would pick autophagy, via TFEB and lysosome production. He adds that you can't fix an old house with just a plumber; mTOR matters because it touches everything. In worms, the benefit runs mostly through autophagy; in yeast, through protein translation. Kaeberlein increasingly credits reduced sterile inflammation for the organ-level benefits in mammals. Attia points out there's no good clinical biomarker of autophagy.

EXAMPLES

• Dog Aging Project trial

The TRIAD trial is enrolling 580 healthy dogs aged 7+ and weighing 40–110 lb, on 0.15 mg/kg weekly or placebo for three years. It's powered to detect a 9% lifespan change, with results expected around 2026. Sabatini says he'll take rapamycin if it's positive. Kaeberlein worries the dose may be too low; ITP mice got roughly the human equivalent of 0.1 mg/kg per day.

• Attia's patients

Attia describes two high-risk patients on 5–8 mg weekly whose blood amyloid (C2N) scores improved. He stresses that's anecdotal and may not reflect the brain. Kaeberlein notes that inhibiting mTOR in the liver rescued a mouse brain disease, so effects outside the brain may matter.

• Mouth-sore fix

Sabatini wonders why no one uses FK506 or inert FKBP-binding mouthwashes to occupy the binding sites in the mouth.

Kaeberlein would rather test rapamycin mouthwash for gum disease.

- **Lab accident**
  Sabatini has never taken rapamycin, apart from inhaling the powder while purifying mTOR without gloves.

OTHER RELEVANT

- **Avoid compounded rapamycin**
  Without an enteric coating, stomach acid can leave bioavailability near zero. Branded or generic sirolimus costs about $5/mg. Some users take grapefruit juice to raise blood levels.
- **Ovaries vs. sperm**
  Short courses restored fertility in older female mice but impair sperm production in males. A Columbia trial is testing it in women with premature ovarian failure.
- **Brain penetration**
  In Sabatini's experience, brain inhibition needed repeated doses; once-weekly doses probably don't reach the brain much.
- **Marmoset data**
  Adam Salmon's ongoing primate study hints at a survival benefit, though in captivity.

252 Latest insights on Alzheimer’s disease, cancer, exercise, nutrition, and fasting

Guest: Rhonda Patrick
Date: 2023-05-01 · Duration: 2:53:27
URL: https://www.youtube.com/watch?v=zkp0DRUQ33g

KEYPOINTS

• Patrick increasingly sees blood-brain barrier breakdown as an early driver of dementia, ahead of amyloid.

Patrick, who carries one APOE4 allele and has Alzheimer's and Parkinson's in her family, cites work by Berislav Zlokovic (USC) and Axel Montagne (Edinburgh). Their research found markers of barrier leakage decades before cognitive decline, in more than half of dementias, independent of amyloid and tau. A leaky barrier lets substances like fibrinogen into the brain, where it damages myelin-making cells, and impairs the glymphatic clearance of debris during sleep. It also disrupts GLUT1 transporters, which carry glucose into the brain without needing insulin. That may explain the brain's reduced glucose use better than 'brain insulin resistance' does.

• Type 2 diabetes and APOE4 both damage the barrier, and diabetes is preventable.

Patrick says 50–80% of people with Alzheimer's also have type 2 diabetes. Attia estimates diabetes roughly doubles risk, about the same as carrying one APOE4 copy (two copies raise risk up to about tenfold). High glucose produces advanced glycation end products that damage tiny blood vessels, as in the eyes and kidneys. Attia sees atherosclerosis and cancer as eventually inevitable for humans, but not type 2 diabetes, which he calls 'gasoline on the fire of aging.'

• The omega-3 DHA transporter may be key to barrier health.

In animals, disrupting the DHA transporter MFSD2A causes about 50% barrier breakdown and more than 50% loss of brain omega-3. In humans it declines with age, faster in Alzheimer's and with APOE4, and genetic defects cause small heads and cognitive impairment. Patrick has joined Bill Harris's Fatty Acid Research Institute to study omega-3 and barrier integrity. She calls trials giving 500 mg–2 g to people who already have Alzheimer's far too little, too late. EPA may help through inflammation; small trials suggest EPA helps depression.

• Blood pressure damage builds up over a lifetime.

About half of US adults and about 20% of 18–39-year-olds have hypertension. Patrick says high blood pressure in midlife, before about 50, is linked to dementia, while starting at 70–80 is much less so. She aims for systolic below 130; Attia cites SPRINT's 120. Exercise and sauna both lower blood pressure, and some people are genetically salt-sensitive.

• Patrick trains hard specifically to raise lactate for her brain.

Lactate, once seen as waste, is used by the brain as fuel and as a signal. George Brooks's 'lactate shuttle' work shows it raises VEGF, which repairs and grows vessels at the barrier, and BDNF, which supports neuroplasticity. Patrick does Tabata-style intervals (16 rounds of 20 seconds on, 10 off) on a Peloton five days a week, reaching about 7–8 mmol. Attia combines zone 2 rides at about 1.9 mmol with 4-minute all-out VO2 max intervals reaching 15–16 mmol, describing fitness as a pyramid needing a wide base and a high peak. He suggests she rest completely in the 10-second off periods to push the 'on' periods harder, and that blood flow restriction training can also spike lactate.

• Exercise and cancer: real but more modest, with stronger effects after diagnosis.

Studies of Olympians found they lived about 5–6 years longer than the general population, about two of those years from fewer cancer deaths. In observational data, aerobic exercise is linked to roughly 10–20% lower risk of breast and colorectal cancer. After diagnosis, active patients had about 50% lower mortality and recurrence. Patrick thinks preventing cancer may require more exercise, toward the upper end of the guidelines (300 minutes a week of moderate exercise), than heart benefits do. One proposed mechanism: shear stress from fast blood flow kills circulating tumour cells. Trials show exercise reduces them.

• Both changed their minds on protein: muscle matters more than results in lab mice.

Low-protein longevity results come from mice in sterile labs that die of lymphomas, not from infections, falls or bed rest. Worm daf-2 mutants live longer only by entering a dormant state humans don't have. Stuart Phillips's newer tracer studies suggest a minimum of about 1.2 g/kg, not 0.8, and more for older or active people because of anabolic resistance. Attia targets about 1 g per pound (2.2 g/kg), spread over four meals and snacks of about 40–50 g each. He notes that in Levine's study, protein intake wasn't linked to IGF-1 in people over 65. Attia cites a 70% lower dementia risk with strong versus weak grip.

• Exercise 'forgives a lot of sins.'

Patrick's continuous glucose monitor as a new mother showed broken sleep pushing her glucose into the prediabetic range. Exercise largely blunted this for about 48 hours. She also cites data where poor sleep raised mortality only in inactive people. Because of her APOE4, she drinks rarely. Attia argues no amount of alcohol is healthy and the J-curve is due to confounding, though harm at a few drinks a week is probably too small to measure. He says APOE4 carriers are more vulnerable, partly through poorer sleep.

EXAMPLES

• Fitness vs questionnaires

In a decades-long study, women with the highest measured cycling fitness had dramatically lower Alzheimer's risk. Studies based on self-reported activity often find no link.

• Sauna routine

Patrick uses 175–180°F for 20–30 minutes after workouts, often rehearsing talks because she finds she remembers them better. She uses a hot tub at night for sleep, and avoided heat during pregnancy because of neural-tube concerns.

• Time-restricted eating

Eating one meal a day usually means too little protein. Attia adds low-calorie protein snacks outside the eating window. Patrick still values not eating late, since melatonin impairs glucose handling.

• GLP-1 drugs

Attia insists on high protein for patients on semaglutide or tirzepatide. Some patients barely eat and lose muscle.

OTHER RELEVANT

- **Vitamin D trials**
  Attia argues trials should dose to a target blood level, as blood-pressure trials do, rather than give a fixed dose.
- **Precision nutrition**
  Patrick expects gene-diet interactions, for vitamin D, omega-3 and sodium, to become clearer within a decade.
- **Alcohol and breast cancer**
  Patrick notes women fear hormone therapy far more than regular drinking, though she says drinking raises breast-cancer risk more.
- **Ketones and lactate**
  Both use the same brain transporter. Patrick hopes for more research in brain injury and Alzheimer's.

248 OUTLIVE book: A behind-the-scenes look into the writing of this book, motivation & main themes

Guest: Bill Gifford
Date: 2023-03-28 · Duration: 1:58:07
URL: https://www.youtube.com/watch?v=Kx8Tag0Qwmw

KEYPOINTS

- **The title 'Outlive' replaced earlier working titles and was never seriously questioned.**
  Attia's first idea in 2016 was 'The Longevity Manifesto', scrapped almost immediately; the working title while shopping the proposal was 'The Long Game'. 'Outlive' stuck because it is simple, evocative and an action — outliving your expectations, your parents or your grandparents, the idea that your fate isn't set in stone. 'The Science and Art of Longevity' was added because, unlike mouse research where definitive experiments are possible, human longevity requires judgment under uncertainty.
- **The book took about six years and went through three distinct versions.**
  Version one was Attia writing alone in 2016, submitting a first section of just under 40,000 words. Version two was written with Bill Gifford from early 2018 to early 2020. In February 2020 the project was effectively dead — the publisher dropped it — until Michael Ovitz asked about it around Christmas 2020, read the long manuscript in two weeks, and helped revive it with a new publisher and editor through 2021–2022.
- **The final structure has three parts that build on each other.**
  Part one explains 'Medicine 3.0', the vehicle for pursuing longevity. Part two covers the diseases that come to take us — the 'horsemen' of heart disease, cancer, neurodegeneration and metabolic disease — because you can't delay them without knowing the enemy intimately. Part three covers the tactics. Attia says that architecture didn't really crystallize until around 2019.
- **Centenarians revealed the strategy: delay every chronic disease.**
  While working on the centenarian chapter, Attia and Gifford realized it isn't a mystery how people reach 100 when most reach 80: they get heart disease much later if at all, cancer much later or never, and neurodegenerative disease later or never. That became the ball game — Medicine 2.0 waits for disease and drags you through it, while Medicine 3.0 acts years earlier.
- **Objective, strategy, tactics — in that order.**
  Attia argues most people jump straight to tactics, such as taking 27 supplements to 'hack' something, without a clearly stated objective. If you can't state the objective, there's fog around everything. His favourite chapter-opening quote is Sun Tzu's: strategy without tactics is the slowest route to victory; tactics without strategy is the noise before defeat.
- **Frameworks are meant to outlast the specific science.**
  Asked how a book can still apply in 10 years, Attia says tactics will change — he will likely take things in a decade he doesn't know about now, and drop things whose evidence turns out weak — but each tactic should anchor back to the strategy. A framework-focused book is more timeless than a list of protocols.
- **Cancer screening is where he expects the most change.**
  Attia takes an aggressive posture on screening because treating a cancer at around a billion cells versus 100 billion cells with the same therapy produces dramatically different outcomes. He hopes liquid biopsies will be far better in 10 years. He contrasts guidance like a colonoscopy every 10 years — which he says fewer than 40% actually get — with his own practice: at 50 he'd already had three, every three years.
- **Immune-cell reprogramming excites him but isn't ready.**
  Something he deliberately left out as too early is reprogramming immune cells, which he considers much easier to reprogram than organs like the heart or liver.
- **Learning to 'kill your babies' was the hardest writing lesson.**
  Attia recalls advice from a lab colleague (he thinks Dan Powell) that you throw out 90% of what you know. As a scientist he struggled to believe readers could appreciate the tip of the iceberg without everything beneath it; the manuscript reached about 190,000 words a year before publication and had to be cut hard.
- **The book reflects his evolving thinking, including emotional health.**
  Attia notes that a version written five years earlier would have contained nothing on emotional health. There isn't a lot on it, but it's there and he believes it's relevant — part of how the podcast interviews and patient conversations shaped the book.

EXAMPLES

- **The 7-out-of-10 cover**
  Exhausted, Attia was ready to accept a cover he rated a solid seven out of ten. Gifford insisted they'd worked too hard for that; a designer produced about 30 covers within three days, each picked a top five or six, and the final design was in everyone's list, for different reasons.
- **The marathon analogy**
  Attia compares the final stretch to a marathon: physiologically you hit the halfway point around mile 20, so the last 6.2 miles hurt as much as the first 20. The last nine months of edits were similarly more work than everything before.
- **Reading the audiobook himself**
  Following Sam Harris's old advice to read edits aloud, Attia narrated the audiobook — and in doing so made several hundred line edits late in the process, to his team's dismay. A director reminded him an audiobook must sound slow at 1x, since he usually listens at 1.8–2x.
- **Talks road-tested on patients**
  Many of the book's explanations come from conversations Attia has with patients repeatedly; some versions land better than others, and he would sometimes ask patients whether he could use their stories.
- **The final chapter**
  The 17th and final chapter, initially disliked by Gifford and editor Diana, became the most improved — Gifford's favourite by

the end.

OTHER RELEVANT

- **Define your objective before choosing tactics.**
  Before adding a supplement or protocol, state what you're trying to achieve and which strategy it serves; if you can't, drop it.
- **Think in terms of delaying all chronic diseases.**
  The centenarian lesson suggests prevention should target heart disease, cancer, metabolic disease and neurodegeneration together, years before symptoms.
- **Discuss earlier and more frequent cancer screening with your doctor.**
  Attia's case rests on catching tumours at far smaller cell counts; his personal colonoscopy cadence is more aggressive than standard guidelines and is his choice, not a universal rule.
- **Expect tactics to change.**
  Hold specific protocols loosely: evidence will strengthen some and undercut others over a decade.

234 Chris Hemsworth on Limitless, longevity, and happiness

Guest: Chris Hemsworth
Date: 2022-12-12 · Duration: 1:16:17
URL: https://www.youtube.com/watch?v=n_jhqgWNKFA

KEYPOINTS

• Limitless grew into something more personal than planned.

Darren Aronofsky called Hemsworth about a six-episode docuseries on longevity. The core team met in New York around November 2019, and shooting began in January. Hemsworth had never hosted anything and worried about seeming genuine. Attia, the show's medical adviser, saw him give more of himself as trust grew. Hemsworth says the risks felt safer once he believed he wouldn't be exploited.

• A 3–4-day fast is a 'reboot,' but expect to feel rough.

Attia explains why the fast was four days: three to four days is roughly the point at which the body meaningfully changes how it handles the absence of nutrients. He normally wouldn't take a patient past three days, but production pushed it to four. Hemsworth also worked out daily and learned breath-holding and spearfishing while fasting. Attia warned there would be stretches of sluggish, grouchy mood.

• Ocean cold is a different stress from an ice bath.

In Norway the water was about 36°F. Their first swim lasted about four and a half minutes, longer than any ice bath Hemsworth had done, in snow and wind and while treading water, which removes the thin warm layer that forms around a still body in a tub. He says it was more a grit test than adaptation, and he relied on coach Ross Edgley's voice. For comparison, Attia has done long swims at about 49°F and calls even that a huge difference.

• Joy comes from contrast.

Attia describes the post-swim euphoria as a 'temporal juxtaposition' of being very low and then very high. We don't feel speed, only acceleration, and he argues emotions work the same way: constant bliss wouldn't feel like profound joy. Hemsworth still makes time for 30–60 seconds of cold water even on busy days.

• Lift heavy, start early, never stop.

Hemsworth seems genetically inclined to be muscular and explosive; he says he grew quickly once he started training while playing footy at 17. Attia tells patients that heavy loads recruit fast-twitch (type 2) fibers, which decline with age. The strength episode moved from dragging a car (Edgley had done a similar feat for about 20 hours) to a 100-ft rope climb from a cable car about 1,000 ft above the Blue Mountains, a better test of grip, strength and top-end fitness. Edgley's advice: be strong, not heavy.

• APOE4/E4 raises Alzheimer's risk sharply but isn't destiny.

Blood work from December 2019 showed Hemsworth carries two copies of APOE4. Attia puts the risk at roughly 8–10 times the general population. Only about 1% of people carry two copies, and about 20–25% carry at least one. Attia had seen only about three such patients, and two suspected it from family history. He told Hemsworth the gene is not deterministic, that earlier action means more risk reduction, and that it could be 'a blessing' as motivation. Attia calls the view that nothing can be done 'complete nonsense.'

• Sauna is a passive cardiovascular stressor with consistent, though not fully proven, data.

In a sauna at about 195°F, Hemsworth's pulse started around 64 bpm. Attia explains that the heart pumps harder to move blood to the skin for cooling, much like exercise. He notes the studies point strongly in the same direction even if the case isn't proven like some interventions. Hemsworth and his wife Elsa have a sauna and ice bath at home, which he calls the best recovery tool.

• Labeling arousal as excitement changes performance.

Hemsworth used to feel like throwing up before auditions and could barely think on set. He read about research in which performers had the same physical arousal (raised pulse, clammy hands, shortness of breath) whether they called it fear or excitement. He decided the feeling meant 'Spidey senses up.' He believes fear pushes and purpose pulls, and both are needed. Fear, he says, keeps him self-deprecating and humble.

EXAMPLES

• Climbing the rope

Hemsworth had never climbed a rope. He trained on a 10-ft rope at home, repeatedly going three-quarters of the way up and jumping off. For about two and a half weeks he stopped lifting and cut calories, dropping a couple of kilos. The real rope, three to four times longer than anything he'd trained on, took about a couple of minutes. His quads, especially his right leg, burned worse than his forearms, and afterward his fingers were locked into claws.

• Imagining his death

In the final episode, palliative-care physician BJ Miller had him live as an octogenarian for three days and picture his last moment. His mother had recently told him that, when she thought she was dying, she felt only gratitude. He realized he wasn't ready, and that the scene he pictured, family and friends in his living room, happens every other weekend.

• Getting Thor

He auditioned for Thor and got no callback, while his younger brother Liam made the final six. Joss Whedon and Drew Goddard, who were working with him on Cabin in the Woods, were baffled. Casting reopened and he auditioned again for Kenneth Branagh, this time without putting anyone on a pedestal or trying to please, and won the part.

• Rush

Ron Howard thought he wouldn't fit in a Formula 1 car. Hemsworth studied interviews with James Hunt, styled his hair like Hunt's, practiced the accent and won the role. Attia jokes that he has watched it so many times Hemsworth should be paid per viewing. Hemsworth hasn't watched it since the premiere.

OTHER RELEVANT

- **Learn your APOE genotype.**
  Attia wishes everyone knew it early, because it shapes prevention around exercise, sleep, metabolic health and more.
- **Use contrast and discomfort deliberately.**
  Short cold exposures, hard climbs and fasting can build resilience. Long fasts beyond about three days deserve medical oversight.
- **Relabel pre-performance nerves.**
  Treat a racing heart as readiness, not threat.
- **Curate your work.**
  Hemsworth wants more time to prepare and decompress between films, working with directors such as George Miller who stretch him, rather than taking roles just for the paycheck.
- **Notice what you already have.**
  The meaningful moments may already be here; change your attention, not just your circumstances.

204 - Centenarians, metformin, and longevity | Nir Barzilai, M.D.

Guest: Nir Barzilai
Date: 2022-04-25 · Duration: 2:48:00
URL: https://www.youtube.com/watch?v=Hbguf9GCdwI

KEYPOINTS

• Genes matter more the further out you go.
Nir Barzilai, an endocrinologist at Albert Einstein College of Medicine who studies centenarians, says twin studies put lifespan heritability low (around 20%), but for reaching 90 or 100 versus 70 or 80, genes play a much larger role. His cohort, begun in 1998, is mainly Ashkenazi Jews, chosen because a population bottleneck and isolation made their gene pool homogeneous and easier to study.

• Centenarians often carry 'bad' genes plus protective ones.
Among roughly 15,000 variants studied, 44 centenarians carried variants that by textbook standards should have made them demented at 70 and dead at 80, including Alzheimer's and Parkinson's risk genes. Barzilai's interpretation: protective variants buffer the damage. With some 80,000 rare genotypes in the population and perhaps '50 ways' to longevity, you need very large cohorts.

• Reduced growth hormone/IGF-1 signaling is a major longevity theme.
About 60% of his centenarians have variants that impair the GH/IGF-1 pathway (including FOXO3A-related genes); in one genotype, people reach normal height after puberty but keep low IGF-1 for life (about 12% of centenarians). Using UK Biobank data on about 440,000 people, they found high IGF-1 in younger people predicted outcomes differently, an example of how the 'right' level may depend on age.

• Growth hormone is a poor anti-aging drug.
Barzilai and Attia agree that GH is unlikely to be geroprotective; people taking it often also take metformin and exercise, so observational benefits are confounded.

• APOE2, CETP and TSH variants show up repeatedly.
APOE2, as allele frequency or homozygosity, is the most validated longevity genotype. CETP variants giving HDL as high as 130–140 mg/dL were an early finding. Centenarians also tend to have higher TSH (mild hypothyroid tendency), and Barzilai explains the thyroid feedback loop for listeners. Lp(a) is a counterexample: high levels in about 10% of the population cause damage that dwarfs other effects.

• Centenarians get sick later and die quickly.
Their 'superpower' is delaying disease by roughly 20–25 years. In controls aged 60–80, only about 10% are disease-free at 80, while about 30% of centenarians past 100 have no disease and take no treatment. A centenarian might have a first heart attack at 101 and die six months later, a compression of morbidity rather than a long decline.

• Metformin has an unusual track record.
Used since the 1950s–60s and approved in the US only around 1993, metformin in diabetics is associated with lower mortality than other drugs, and in the Diabetes Prevention Program both metformin and lifestyle prevented diabetes in roughly 30% of participants, a trial stopped early. Attia notes the healthy-user bias: compliant patients are healthier.

• TAME aims to make aging an FDA indication.
The Targeting Aging with Metformin trial plans about 3,000–3,500 non-diabetic participants aged 65–79 across 14 US centers (about 250 each), looking at a composite of age-related diseases. Using a multi-morbidity endpoint means 20–50 times fewer people are needed than a single-disease trial (versus about 12,000), making it much cheaper; the effects in prior studies are consistently 20–30%.

• Biomarkers of aging are the goal.
Barzilai wants tests to tell a 50-year-old whether they're biologically 40 or 60, for example to decide on screening. His group measured 5,000 proteins in 1,000 people to see what changes between 65 and 95, and TAME samples could validate such markers. Volatile metrics like fasting glucose (95 vs. 105 depending on last night's meal) are poor biomarkers.

• Metformin may blunt exercise gains.
Attia, who stopped taking metformin, notes it's a weak mitochondrial inhibitor and that studies show blunted improvements in cardiorespiratory fitness; it may be net positive for some people but not for those who exercise a lot. Barzilai thinks most benefit appears in people recruited above about 50, and that senolytics probably shouldn't be used before 70–80.

EXAMPLES

• The lactate check
In a 1987 study, Barzilai saw lactate rise from below one to above one mmol in everyone who took metformin, consistent with its mitochondrial effect.

• A $2.8 million gift
The American Federation for Aging Research received a single $2.8 million donation to recruit 10,000 centenarians plus offspring and controls, which Barzilai calls a bargain for finding rare protective genotypes.

• The 115-year ceiling
Barzilai puts the human species' lifespan at about 115 years (with outliers like 122), and jokes that if asked when we'll live to 150, the answer is 'in 150 years', because even starting now the experiment takes that long.

• Two VO2 maxes, neither disabled
Attia contrasts people at 30 vs. 50 mL/kg/min VO2 max: neither is 'disabled', but the gap determines what life feels like at 85. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

• Biblical ages
Asked about the long lifespans in scripture, Barzilai mentions an effort to assess whether any age claims from about 2,000

years ago in biblical stories have validity.

OTHER RELEVANT

- **Know your APOE and Lp(a).**
  These genes shape risk; most people lack centenarian genes and must delay disease through behavior and medicine. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Don't take GH for longevity.**
  Despite its popularity in anti-aging clinics, the evidence points the other way; lower IGF-1 signaling characterizes many centenarians. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Weigh metformin carefully.**
  Its benefits may be real for some, especially people with metabolic disease, but it could blunt training adaptations in active people; TAME is meant to settle this.
- **Aim to compress morbidity.**
  The goal is decades of healthspan, not merely more years. Centenarians show it's possible to push the onset of heart disease, cancer and dementia back by two decades; for everyone else, exercise, lipid control and metabolic health are the tools for chasing the same pattern.

202 - Peter on nutrition, disease prevention, and more — looking back on the last 100 episodes

Date: 2022-04-11 · Duration: 1:57:38
URL: https://www.youtube.com/watch?v=LkUPHBhM8Ow

KEYPOINTS

• Strong convictions, loosely held.
Looking back on episodes 100–200, Attia describes holding firm positions while staying ready to change them when evidence shifts. The episode is a tour of where his thinking evolved: cancer, apoB, Alzheimer's genetics, fasting, protein, exercise, NAD, psychedelics and sleep, ending with a long primer on Formula 1.

• His book has been a six-year project.
Begun in 2016, the manuscript had ballooned; his editor hoped for about 80,000 words, and Attia and co-writer Bill Gifford aimed to converge on around 120,000, still thick but manageable.

• Immunotherapy works for a minority, so far.
Checkpoint inhibitors and IL-2 produce durable responses in perhaps 10–20% of people with metastatic melanoma or renal cell cancer. Of cancer deaths, leukemias and lymphomas account for about 20% and solid organ cancers about 80%, so the big task is getting immune-based therapy to work across the solid tumors that make up the rest.

• GI cancers make a strong case for aggressive screening.
Of roughly 600,000 US cancer deaths, about 170,000 are in the digestive system, from mouth to anus. Colonoscopy timing and frequency matter: guidelines say 45–50, Attia had his first at 40–41 and was scheduled for another at 49. Pancreatic cancer lacks good screening, so he uses tools like diffusion-weighted MRI and liquid biopsies, which are imperfect.

• ApoB should be lowered early and far.
Attia argues infantile apoB levels of 30–40 mg/dL are not harmful, and that lowering apoB to 20–30 in everyone from their 20s might nearly eliminate ASCVD. Practically, anyone in their late 30s or early 40s above the 20th percentile should be treated. He uses 60 mg/dL (about the 5th percentile) as a ceiling.

• APOE4 risk is real but modifiable.
Attia's rough figures: E2/E4 is a wash or slight increase; E3/E4 confers about a 2–3-fold risk of Alzheimer's; E4/E4 about 8–12-fold (maybe 8–10). At the individual level many E4 carriers never develop disease, and other genes modify that risk.

• Time-restricted eating mostly works by eating less.
Attia now thinks the benefit of TRE comes largely from calorie reduction, not timing: 3,000 calories over 12 hours vs. 6 hours likely differ little. It can be problematic when people lose lean mass along with fat, so the scale improves while body composition worsens.

• Most people under-eat protein.
Attia calls the RDA of about 0.8 g/kg 'out to lunch': for an 80-kg (about 175-lb) person that's around 65 g a day. He believes the RDA reflects the minimum to avoid deficiency, not what's optimal for building and keeping muscle, especially with age.

• Exercise is the most potent longevity tool.
Moving from the bottom 25th percentile of cardiorespiratory fitness to the next quartile (low, below average, above average, high, elite) brings large mortality reductions, and the gains continue up the scale. Strength matters even more than muscle mass, though mass is a good proxy.

• He's uninspired by NAD precursors and wary of psychedelic hype.
Attia sees little evidence that NR or NMN extend healthspan. On psychedelics, he thinks they're a powerful therapeutic tool in the right setting but worries about treating them as a cure-all, given how often he hears people raving about a shaman in Peru.

• Trazodone has become his favored sleep aid.
An old antidepressant (a serotonin antagonist and reuptake inhibitor), trazodone caused too much drowsiness at 250–300 mg. At 25–100 mg nightly off-label, Attia says it helps more than 80% of the people who try it and, crucially, preserves sleep architecture, unlike drugs such as Ambien that just render you unconscious. He's also less worried about blue light than the stimulation of what you do on screens.

EXAMPLES

• A new patient at the 99.9th percentile
Attia cites Framingham Offspring apoB percentiles (5th about 62, 10th about 70, 20th about 78, 50th about 97, 80th about 118, 95th about 140) and a new patient whose apoB was around 171, past the 99.9th percentile.

• The 'I lost 5 pounds' trap
A typical 5'11" person who goes from 180 to 175 lb on fasting feels great, but DEXA shows visceral fat unchanged and lean mass down; only the crude scale number improved. A 300-lb person losing 70% fat and 30% lean is still net better off.

• Grip weakness after surgery
Two days after shoulder surgery, Attia noticed his right grip was weaker because he couldn't recruit the full shoulder and scapular musculature, an illustration of how connected the kinetic chain is.

• Senna's qualifying record
In the F1 section, Attia praises Ayrton Senna's more than 60 pole positions in 161 races and recalls mid-1980s McLarens boosted to as much as 1,400–1,600 horsepower in qualifying versus about 800 in races.

• F1 tires and pit stops
Each tire change costs a guaranteed 25–26 seconds; with 10 teams and 20 drivers, strategy around soft and medium compounds and qualifying (Q1 cuts five, Q2 sets 11–15, Q3 decides the top 10) often decides races.

OTHER RELEVANT

- **Screen GI cancers aggressively.**
  Consider colonoscopy earlier and more often than minimum guidelines, discussed with your doctor. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Eat more protein than the RDA.**
  Aim well above 0.8 g/kg, especially during weight loss, to protect lean mass. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Check body composition, not just weight.**
  Use DEXA or similar to make sure fat, not muscle, is what you're losing.
- **Treat sleep drugs by their effect on architecture.**
  If a sleep aid is needed, ask a clinician about options that preserve deep and REM sleep.
- **Climb the fitness percentiles.**
  Every step up in VO2 max and strength pays off. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

175 - The biology of aging, rapamycin, and other interventions that target the aging process

Guest: Matt Kaeberlein
Date: 2021-09-13 · Duration: 2:49:45
URL: https://www.youtube.com/watch?v=_vsNw-OCciU

KEYPOINTS

• Targeting aging itself could add far more healthy years than curing diseases one by one.
Kaeberlein, an aging biologist at the University of Washington, notes that roughly a dozen or 15 interventions now extend mouse lifespan by 15–30%. Extrapolated to humans, that is about 20 years of life expectancy, and because all functional declines slow together, those years are spent in relatively good health. He calls the disease-by-disease approach '20th-century medicine' and contrasts it with targeting the biology of aging.

• Aging is the dominant risk factor, and it can't be offset by perfect health.
A 70-year-old with every risk marker in their favor still has a worse 10-year mortality outlook than a 20-year-old 'train wreck'. Kaeberlein and Attia agree that any 50-year-old is functionally impaired compared with themselves at 25, which is why they argue regulators shouldn't treat typical 65–70-year-olds as 'healthy' when weighing trial risk.

• Centenarians get the same diseases—just decades later.
Citing the centenarian studies of Nir Barzilai and Tom Perls, Attia notes that centenarians don't live longer with chronic disease; they get a 20–30-year phase shift in onset. They are more likely to carry protective variants such as APOE2 rather than APOE4. Attia's clinical takeaway: the earlier prevention starts, the more you can mimic that delay.

• Rapamycin is the best-supported longevity drug, but human dosing is guesswork.
It extends lifespan in mice even when started late in life. Kaeberlein wouldn't start it before about age 25, and admits 'we're flying blind' on dose and frequency. In their mouse study, three months of treatment between 20 and 23 months of age produced lifespan effects roughly similar to continuous treatment in the National Institute on Aging's Interventions Testing Program (ITP).

• The Novartis vaccine studies are the key human evidence.
Joan Mannick and Lloyd Klickstein's 2014 study at Novartis gave older adults (65+) the rapalog everolimus—placebo, 0.5 mg daily, 5 mg weekly or 20 mg weekly. Low-dose arms improved response to a flu vaccine, which Attia used to infer that a moderate weekly dose is the sweet spot. Old mice show a similar problem: only about a third respond adequately to vaccines.

• The follow-up trials were promising, then the phase 3 failed.
A phase 2 trial combining everolimus with RTB101 (a catalytic mTOR inhibitor specific to complex 1 at the doses used) reported improved vaccine response and fewer upper respiratory infections, though the everolimus-only arm missed significance. The company, resTORbio, then tested RTB101 alone in a phase 3 against respiratory illness; it missed endpoints, was stopped early, and the company merged with a CAR-T firm. Kaeberlein calls the endpoint noisy rather than proof the approach fails.

• Side-effect fears are overstated at these doses.
Kaeberlein argues that claims of significant side effects are 'blatantly false' at the doses tested—there's no evidence of major harm from rapamycin, everolimus or RTB101 monotherapy in healthy people—though he concedes we lack long-term controlled trials, so the true risk-benefit balance remains unknown.

• Periodontal disease would be a smarter trial endpoint.
His lab found that eight weeks of rapamycin reverses the defining features of periodontal disease in aged mice. About two-thirds of older adults have or will get periodontal disease, which is linked to dementia, cardiovascular disease and diabetes, so a short trial with a dental exam could give a cleaner signal.

• Epigenetic clocks and telomeres are not yet useful aging measures.
Attia finds clocks easily moved by short-term interventions of doubtful biological relevance, comparing them to glucose of 110 after a bad night's sleep versus 95 after a good one. Kaeberlein explains clocks are DNA chemical marks that track chronological age; both consider telomere length unhelpful for organism-level aging.

• mTORC1 versus mTORC2 explains some side effects.
Rapamycin binds FKBP12 and mainly inhibits mTOR complex 1; most lifespan evidence points to complex 1. Higher or chronic doses may affect complex 2, linked to glucose-intolerance effects in mice. Yet data shared by a physician prescribing rapamycin showed triglycerides falling from about 200 to 70 mg/dL and improved glucose in prediabetic patients—uncontrolled, so caution applies.

• NAD precursors remain unproven.
NR and NMN raise NAD and sometimes show benefits in animals, but many results—including from the ITP—don't replicate, and NR and NMN camps dispute each other's bioavailability. Because supplements can be sold without trials, Kaeberlein expects no definitive human study and would be more bullish only if NR slowed aging in dogs.

EXAMPLES

• Kaeberlein's frozen shoulder
Unable to play catch with his son, he was diagnosed with frozen shoulder and told little could be done. He tried eight-to-ten-week rapamycin courses (about 8 mg weekly) and recovered roughly half his range of motion within eight weeks and later most of it—an anecdote, not evidence.

• The Dog Aging Project
The TRIAD trial aims to randomize 350 middle-aged dogs of 40–100 pounds, 175 per arm, to rapamycin or placebo over three years, powered to detect a 15% change in lifespan—possibly the first clinical trial with lifespan as its endpoint. An earlier 24-dog safety study (16 rapamycin, 8 placebo) showed improved heart function on echocardiograms.

• Sex differences in mice
In the ITP, low-dose rapamycin extended lifespan about 14% in females and 9% in males; at higher doses males caught up,

and some very high doses began to reverse benefit in females.

- **Leigh syndrome mice**
  In a mouse model of this childhood mitochondrial disease, which normally lives about 55–60 days, rapamycin roughly doubled or tripled survival and prevented brain lesions.

OTHER RELEVANT

- **Treat rapamycin as experimental.**
  Dosing, frequency and long-term risks in healthy humans are unknown; anyone considering it needs a physician's supervision and should weigh benefits against uncertainty.
- **Start prevention early.**
  Centenarian data suggest delaying disease onset is the realistic goal, and the earlier risk reduction begins the larger the delay.
- **Be skeptical of biological-age tests.**
  Single clock readings can swing with short-term factors; don't make decisions from them yet.
- **Don't assume supplements work because they're sold.**
  NAD boosters lack replicated evidence of slowing aging.

171- Longevity science: caloric restriction studies, aging biomarkers & possible longevity molecules

Guest: Steven Austad
Date: 2021-08-09 · Duration: 2:34:59
URL: https://www.youtube.com/watch?v=WNKRSiSGvGE

KEYPOINTS

• Lower extrinsic danger leads to slower aging

Austad's first aging study compared opossums on Sapelo Island, off Georgia, which has few predators, with mainland opossums. Mainland opossums, about the size of a small cat, got cataracts by around 18 months and declined fast. The island animals aged more slowly, which fits evolutionary theory: species that face less outside death evolve to age more slowly.

• The lab mouse is a strange, narrow model

Lab mice descend from 'fancy mice' bred for odd coat colors and sizes, then inbred until every animal is genetically identical at every locus. Austad compares this to testing drugs on the same set of twins over and over, out of about 4,500 mammal species. That's why he values the Interventions Testing Program (ITP), which uses genetically heterogeneous mice at three sites.

• Calorie restriction works in lab rodents, but the effect is weaker in wild mice

The finding dates to rat work in the 1930s, whose author never seemed to grasp its importance and later moved into high-protein bread for the military. Austad brought wild-caught mice into the lab and restricted them to 70% of normal intake. For most of their lives there was no benefit. Only the last ~20% of survivors lived longer, so he expects the effect to be much smaller than in obese, sedentary lab strains.

• The two monkey studies disagreed partly because of sugar

The Wisconsin study used a purified diet that was about 28–29% sucrose. The NIA (Bethesda) study used natural ingredients with about 3% sucrose. Wisconsin restriction extended life compared with controls, but the NIA study's controls were healthier to start with, and restriction added little. Austad likens Wisconsin to 'three Big Macs, two monster fries and two jumbo Cokes a day' versus 70% of that: eating less toxic food will look good. He suspects the restricted Wisconsin monkeys had more diabetes than the NIA controls.

• Captive animals, including us, are obese compared with wild relatives

Both captive monkeys and modern humans differ from their wild counterparts. Austad's conclusion is that nutrition and aging questions ultimately have to be studied in humans.

• Human calorie restriction is very hard to sustain

The CALERIE trial aimed for about 25% restriction, but people managing their own food reached only about 11–12% over two years. Austad says only about 30% of Calorie Restriction Society members truly sustain it, with BMIs around 17–20. Those trials were also in people in their late 30s, and what's good for them may not suit people in their 60s.

• Time-restricted eating and fasting may matter more than total calories

Mouse work suggests that going many hours a day without food may account for as much of the benefit as eating less. A short fast of two or three days before surgery sped recovery in mice in the late Jim Mitchell's work, including after an ischemia-reperfusion injury. Peter and Austad also discuss 16-hour eating windows and the five-day fasting-mimicking diet of about 750 calories a day.

• Women outlive men at every age, except when it comes to Alzheimer's

Women survive better as infants and in their 20s, 30s and 40s, and die at lower age-adjusted rates of every major cause except Alzheimer's disease. Austad offers a 'private hypothesis' that Alzheimer's will turn out to have an autoimmune component, since women are more prone to autoimmune disease.

• Sex differences in ITP drug results may reflect dosing

Rapamycin favors females at low doses, a gap that shrinks as the dose rises. 17-alpha-estradiol, acarbose and canagliflozin mostly help males. Austad suspects higher blood levels in females may mean they're effectively overdosed. Peter notes that the canagliflozin and acarbose results point to glucose dynamics rather than eating less.

• Validated aging biomarkers are the biggest missing tool

The NIA put about $100 million into aging biomarkers in the 1990s without success. Austad wants markers that answer in weeks or months, across ages, so that healthy people can learn how to stay healthy without decades-long trials.

EXAMPLES

• From cab driver to lion tamer

Austad drove a New York cab in the gritty mid-1970s, then drove to LA, where a film producer hired him on the spot to care for 25 lions. One lion clamped onto his leg over food. He later went to graduate school planning to study lions, and ended up studying opossums.

• Biosphere 2

In this early, involuntary human calorie-restriction experiment, Roy Walford entered at about 66 and left at 68. He was an outlier, since most participants were young, so not much can be concluded.

• The 150-year bet

About 21 years earlier, Austad bet Jay Olshansky that the first person to live to 150 was already born by 2000. The record, Jeanne Calment, is about 122.5 years, and nobody has reached 120 since. Austad stresses that he wasn't predicting average life expectancy of 150. He sees 100 as conceivable.

• Intermittent mTOR inhibition in humans

Austad cites the everolimus study in which 5 mg and 20 mg once a week improved vaccine response in older people, with the lower dose working just as well. This supports intermittent dosing that targets mTORC1 while sparing mTORC2, whose inhibition may cause side effects.

OTHER RELEVANT

- **Rapamycin and metformin each have only half the case**

  Austad's view: 'If we go by the mouse data it would have to be rapamycin; if we go by the human data, metformin', and he calls both weak statements. He finds rapamycin plus metformin interesting. Most clinical trials fail because they're built on mouse data.

- **Be intrigued, not excited, by single mouse studies**

  He wants more human data before getting excited about SGLT2 inhibitors or NAD precursors. SGLT2 human data on kidney failure, heart failure and mortality are impressive, but they come from people with disease, not from longevity trials.

- **It's never too late to improve**

  Austad stresses that a 50-year-old who has never exercised and has eaten badly can still benefit from changing course.

#148 - Richard Miller, M.D., Ph.D.: The gold standard for testing longevity drugs: the ITP

Guest: Richard Miller
Date: 2021-02-08 · Duration: 2:14:25
URL: https://www.youtube.com/watch?v=g8bXYKeeWnc

KEYPOINTS

• The Hayflick limit sent aging research down a side road
Normal human cells in culture divide about 50 times and then stop. Miller says many excellent cell biologists spent their careers on this 'Hayflick system' believing they were studying aging. He thinks it has little to do with why organisms age.

• The key question is whether aging can be slowed, and it can
Before the 1990s many believed aging 'is what it is.' Cynthia Kenyon's 1993 daf-2 work in C. elegans showed that single genes (daf-2 resembles the IGF receptor, daf-16 resembles FOXO) can greatly extend lifespan. That came the same year a Nature paper argued no single gene mutation could do so. Miller argues that aging is at least partly a single process a drug might slow, not a 'spaghetti bowl' of 30–50 separate ones. He once had a friendly fight about this with George Martin.

• The ITP is built for statistical power and generality
The Interventions Testing Program runs each drug at three sites: Jackson Labs, Miller's lab in Michigan and Randy Strong's lab at UT San Antonio. Each year each site has 50 males and 50 females per drug and 100 controls of each sex. That's enough to detect a roughly 8–10% lifespan change with 80% power. Anyone can suggest a compound, and a steering committee, advised by five outside scientists, chooses.

• Genetically heterogeneous mice are the point
About 90% of mouse research uses a single inbred genotype, usually 'Black 6', where every mouse is identical. In the ITP's four-way cross, no two of the more than 20,000 mice are the same, though any two share half their genes. Results are more likely to generalize. The NIA stopped supplying such mice for lack of demand.

• Rapamycin works even when started late, in both sexes
In the second cohort (started 2005), 90–95% of oral rapamycin was destroyed in the stomach. Reformulating it with a coating took a year, so treatment began at 19–20 months, roughly a 60-year-old human. By then 15–20% of males had already died. Rapamycin still extended lifespan strongly in both sexes and remains the only drug with a very strong effect in females. Peter cites 90th-percentile lifespan gains of about 9% in males and 14% in females.

• Acarbose and canagliflozin probably work by blunting glucose spikes
Acarbose, suggested by David Allison and Daniel Smith as a calorie-restriction mimic, blocks starch digestion and works mainly in males. Canagliflozin, an SGLT2 inhibitor, also blocks peak glucose and also extends life mostly in males. That supports the view that cutting post-meal glucose peaks, not eating less, is the mechanism.

• 17-alpha-estradiol helps only males
This weak, non-feminizing form of estrogen extended male lifespan, and Peter and Miller compare a 14.4 ppm dose with a lower one. In another lab, males started at 16 or 20 months got stronger muscles and better glucose tolerance; females didn't. Female mice already outlive males, and their estrous cycles stop around 8–11 months.

• Negative results are valuable
Resveratrol failed at doses about 3–10 times higher than in David Sinclair's original paper (Miller wasn't sure of the exact multiple). Green tea extract, curcumin and methylene blue also failed. Miller notes that drinking enough wine to match the mouse dose would take about 600 bottles a day. No ITP drug has significantly shortened lifespan.

• Starting late and measuring the tail are tougher, fairer tests
Starting a drug when 35–40% of animals have already died asks a lot of it. Miller considers age at the 90th percentile of survival more informative than percentage change in median lifespan, because it shows whether a drug delays death in already-old animals. Rapamycin, 17-alpha-estradiol and acarbose all still work when started in middle age. In rapamycin mice, tissue changes in organs such as the adrenal gland resembled those of younger controls.

• Metformin's failure in mice isn't the final word
Metformin alone didn't extend lifespan in the ITP; it worked only when paired with rapamycin, which may just be the rapamycin. Miller lists reasons: mice and people are organized differently, it was tested at one dose with continuous dosing, and a different dose or schedule might work. Observational data showing diabetics on metformin outliving non-diabetics justify the human TAME trial, he says.

EXAMPLES

• Aspirin in the first cohort
Aspirin was among the first four ITP compounds, along with NDGA and nitroflurbiprofen. It was given at a dose approximating a human baby aspirin. It initially showed a male benefit that didn't replicate. NDGA has worked three times, but only in males.

• Hydrogen sulfide donor SG1002
Suggested by a colleague, it increased median male lifespan by about 14% with a 9% maximum extension, and did nothing in females. About 80% of ITP mice die of cancer, a third of it hematologic, whereas humans mostly die with atherosclerosis.

• 'Statistics shopping'
Of a compound reported elsewhere to help male mice, Miller suspects the authors tried the standard log-rank test, failed, then picked a test that weights early deaths and got p = 0.046.

• Nicotinamide riboside
Tested at the supplier's suggested dose (the company agreed to publication either way), NR didn't extend lifespan. The team also couldn't show consistent NAD changes in brain, muscle or heart, possibly because NAD turns over in seconds to minutes.

OTHER RELEVANT

- **Use acarbose as a targeted tool, with caution**

  Peter says he has used about 100 mg of acarbose as a 'cheat meal drug' before pizza to blunt glucose spikes. Too much causes GI distress.

- **Weight evidence by sex, dose and timing**

  Many ITP effects are sex-specific and dose-dependent. A single dose and schedule that fails isn't proof a drug can't work, and a single mouse result isn't proof it will in humans.

- **Aim for realistic gains**

  Miller and Peter see nothing that suggests immortality, but a 10–15% improvement in human lifespan and healthspan would be a remarkable achievement.

#123–Joan Mannick & Nir Barzilai: Rapamycin and metformin—longevity, immune enhancement, & COVID-19

Guest: Joan Mannick & Nir Barzilai
Date: 2020-08-10 · Duration: 2:16:12
URL: https://www.youtube.com/watch?v=XVA4v0R5PuI

KEYPOINTS

• Mannick moved into aging research at 50 to test mTOR inhibition in humans

Around 2012, at Novartis, Joan Mannick asked to work on aging. Colleagues questioned why she'd give the drug sold to suppress the immune system in the hope of enhancing it. Her reasoning was that inhibiting mTOR had extended life in every organism tested: yeast, worms, flies and, through the NIH's Interventions Testing Program (ITP), mice. A lifespan trial in humans was impossible, so she looked for a measurable human endpoint and carefully dosed the drug to minimise side effects.

• Turning mTOR down, not off, improved immune function in older people

Her 2014 study gave older adults a rapamycin analog (RAD001, everolimus) before a flu vaccine. The two lowest doses, 0.5 mg daily or 5 mg weekly, worked best, better than 20 mg weekly. These doses gave less mTOR inhibition. Exhausted T cells (PD-1 positive CD4 and CD8 cells, which accumulate with age) fell by about 25–30%. Attia calls the paper his '2014 Christmas gift'.

• Low intermittent doses mostly spare mTORC2

Mannick says the low doses mainly hit mTORC1. They caused no real hyperglycaemia or high blood lipids, which are the side effects linked to mTORC2. Her newer compound, RTB101, is catalytically selective and has a 4–6 hour half-life, so once-daily dosing inhibits mTORC1 for only part of the day. She compares it most closely to 0.5 mg of everolimus daily.

• RTB101 reduced respiratory infections in phase 2

In the first phase 2 study, six weeks of RTB101 combined with everolimus looked best. In the second, which lasted 16 weeks in a sicker population, RTB101 alone did better. In both, RTB101 reduced respiratory tract infections, and one phase 2b study showed 52% less severe disease. Mannick's interpretation is that mTOR inhibitors don't prevent infection. Instead, they produce a better immune response so symptoms are milder. Lab-confirmed infections were too few to analyse well.

• Barzilai chose metformin for strategy, not because it's the best drug

Barzilai says rapamycin may be the better drug. Metformin was chosen for TAME (Targeting Aging with Metformin) because it is cheap, safe and generic, and has decades of data, making it a tool to establish aging as a target the FDA can accept. He cites about 30 animal studies in which metformin extended lifespan. The ITP results for metformin alone are mixed. Metformin plus rapamycin produced some of the longest-lived mice in the programme.

• The diabetic-patient paradox

Attia highlights a frequently cited finding: people with type 2 diabetes on metformin lived longer than matched people without diabetes, despite the vascular damage diabetes causes. The guests frame metformin as acting on several interacting hallmarks of aging at once. Barzilai declines to name a single most important mechanism.

• TAME is designed to measure delay of multiple age-related diseases

The trial is powered on 3,000 participants, and the team may expand to 3,500. It runs across 14 centres and includes ancillary studies, some needing only 250 people. Participants take 1,500 mg of extended-release metformin a day, three 500 mg tablets. That is the dose Barzilai takes himself.

• Older people's COVID risk is about comorbidity as much as immunity

Barzilai says people aged 80 and over are about 180 times more likely to die of COVID than 20-year-olds. Attia argues that to make someone resistant you would reduce their comorbidities first, not just raise immunity by 10–20%. Both drugs might help on both fronts. Barzilai criticises ageism in leaving older people to quarantine.

• Commercial aging clocks can mislead

Barzilai points out that clocks combine methylation with blood markers such as glucose, insulin and vitamin D. Correcting a vitamin D level of 20 with 5,000 IU a day could 'improve' biological age, even though no trial has shown vitamin D extends life. He prefers proteomics: in 1,000 people aged 65–95, hundreds of proteins changed with age. In about 500 children of centenarians, around a third of those changes were slowed.

EXAMPLES

• Why Attia stopped metformin

He began metformin in May 2010 at 2,000 mg a day without titrating up, which caused about two months of nausea. Now he titrates patients up from 500 mg at night. In 2018, testing zone 2, defined as the most work he could do with lactate under 2 mmol, he found his resting lactate around 1.6 mmol, unusually high. That raised concern that metformin was hurting his mitochondrial performance, so he stopped.

• Metformin blunted exercise gains in older adults

In a study of people around 75, metformin blunted the improvements from exercise. Barzilai says the gene-expression data showed mTOR transcripts were higher with exercise alone and dampened by metformin. That is consistent with metformin lowering mTOR while exercise raises it.

• Early observational COVID data

Barzilai cited a not-yet-peer-reviewed University of Minnesota analysis of about 6,000 patients. Women on metformin had roughly 21–22% lower COVID mortality, along with lower TNF-alpha. He admits he couldn't tell from the paper whether the effect was limited to people with diabetes. For Chinese data he relied on indirect figures because exact data cost $3,500.

• Rapamycin for Attia since about 2018

Attia wanted to take rapamycin from 2011–2012 based on animal data, but his biggest fear was immune suppression. Mannick's 2014 paper made him bolder, and 5 mg once a week looked like a reasonable starting dose.

- **Centenarians' families**

  The intro cites Barzilai's Longevity Genes Project of more than 500 healthy people aged 95 to over 110, plus their offspring. Barzilai notes centenarians get the same diseases about 30 years later and behave physiologically like much younger people, rather than avoiding disease entirely.

OTHER RELEVANT

- **Separate dosing goals**

  Mannick and Attia discuss using low, intermittent rapalog doses to enhance immunity. High, immunosuppressive doses might help suppress the dangerous late immune overreaction in severe infection. A small Hong Kong influenza study and one hospitalised-COVID trial were the only data cited, so it remains unproven.

- **Titrate metformin**

  If metformin is prescribed, start low (500 mg at night) and build up to avoid GI side effects. Exercisers may want to weigh possible blunting of training adaptations.

- **Prefer trials to associations**

  Barzilai warns that if metformin delays death, observational data may show more people living longer with diseases like Alzheimer's, which is a misleading signal. Only randomised trials settle this.

- **Risk tolerance should update with the situation**

  Attia argues that the stakes in summer 2020 justified a different regulatory appetite for risk than in 2018. Mannick prefers generating data in trials before acting.

#118 – Lloyd Klickstein, M.D., Ph.D.: Rapamycin, mTOR inhibition, and the biology of aging

Guest: Lloyd Klickstein
Date: 2020-07-09 · Duration: 2:14:54
URL: https://www.youtube.com/watch?v=fIAM2YADBbg

KEYPOINTS

• Context: the phase 3 trial later failed

This interview was recorded in September 2019. Attia notes up front that resTORbio's phase 3 trial of RTB101, discussed throughout, was later published and did not meet its primary endpoint. Everything said about that programme should be read with that in mind. Lloyd Klickstein, a rheumatologist and immunologist, left Harvard academia in 2006 for the Novartis Institutes, partly because grant funding had become far more competitive than in the late 70s and early 80s.

• Translational medicine works in both directions

At Novartis, Klickstein set up a 'new indication discovery unit' around 2008–09. It chose projects with real medical need, scientific tractability, and no existing Novartis work (ideally no one else's either). Joan Mannick brought the idea of testing mTOR inhibition against ageing of the immune system and started the project around 2010. Klickstein stresses that observations can move from humans back to animals as well as forward.

• The 2009 mouse study made rapamycin a credible longevity drug

Rapamycin extended lifespan in mice that were already about 600 days old, an age at which caloric restriction no longer extends life. Klickstein cites gains of roughly 15% and 25%. TOR was identified in yeast by Michael Hall's work in 1991 and in mammals in 1994, including by Sabatini. Ilya Mechnikov's work on cells that engulf pathogens (phagocytosis) earned a share of the 1908 Nobel Prize.

• mTORC1 and mTORC2 behave differently

Rapamycin, bound to FKBP12, inhibits mTORC1 but acts unevenly on its targets, more weakly on 4E-BP1 and less still on ULK1, which helps start autophagy. It doesn't directly inhibit mTORC2. With sustained exposure, though, signs of mTORC2 inhibition appear within a week to a month: high blood sugar and high triglycerides. Klickstein says the exact mechanism isn't known.

• Dose and schedule determine whether it boosts or suppresses immunity

The 2014 trial gave adults over 65 the rapalog everolimus (RAD001) in one of three regimens. 0.5 mg daily gave partial, sustained mTORC1 inhibition. 5 mg weekly gave full inhibition for a couple of days. 20 mg weekly fully inhibited it throughout. High doses of rapalogs are immunosuppressive, which is why rapamycin (sirolimus, approved in 1999) is used in transplant patients.

• The 2014 result: a better flu-vaccine response at low doses

The pre-specified target was a 1.2-fold improvement in flu vaccine response for two of three strains, the threshold earlier work linked to fewer symptomatic infections. Both low doses reached it, but 20 mg weekly improved only one strain. Checkpoint proteins such as PD-1, markers of exhausted T cells, fell by about 10–20% on CD4 and CD8 T cells. Adverse events also listed fewer infections over the following year, although influenza alone was too rare to analyse.

• Side effects rose with dose

Attia remembers mouth ulcers as the classic side effect in transplant patients on 2–4 mg daily. In the trial, mouth ulcers affected about 4% of people on 0.5 mg daily or 5 mg weekly, compared with about 17% on 20 mg weekly. Total adverse events rose with dose, from about 35 to 46 to 109 across the three drug arms of roughly 53 people each. That supports the idea of a therapeutic window for low or intermittent dosing.

• The 2018 study added a catalytic inhibitor

In 264 older adults, BEZ235 (later RTB101), an inhibitor that blocks mTOR's catalytic site, and its combination with RAD001 reduced respiratory tract infections. The combination and RAD001 improved flu vaccine response, but RTB101 alone did not. Klickstein clarified that RTB101 is not everolimus combined with something else.

• The phase 2b refined the target population

With 652 patients across southern- and northern-hemisphere cold and flu seasons, 10 mg of RTB101 once daily again reduced respiratory infections. Benefits were seen in people over 85 and those with asthma or diabetes, but not in smokers or people with COPD. It was used to power phase 3, which included a fully enrolled study of 1,024 people aged 65 and over treated for 16 weeks.

• Fasting and rapalogs overlap but aren't the same

Klickstein mentions a mouse study in which 24 hours of fasting before an otherwise lethal ischaemia–reperfusion injury let most or all of the mice survive, while fed mice died. He doesn't know how to extrapolate that to humans, since the metabolic consequences of the fast may matter more than its length.

EXAMPLES

• A Cialis analogy for drug exposure

Attia compares 5 mg daily of Cialis (tadalafil) with 20 mg on demand. The daily dose keeps a narrow gap between peak and trough and causes fewer side effects. A single 20 mg dose overshoots, but lasts two to three days.

• Ketamine activates mTOR

Klickstein calls intravenous ketamine 'almost a miracle drug' for major depression, working in minutes to hours with a large effect size. Its mechanism is unclear, and ketamine has been linked to mTOR activation, the opposite of rapamycin.

• Rapamycin binds more than FKBP12

Attia was surprised to learn that rapamycin binds at least FKBP12 and FKBP51. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

- **Metformin**
  Klickstein calls it a wonderful drug with excellent data in diabetes, plus some retrospective longevity signals in people with diabetes.

OTHER RELEVANT

- **Don't extrapolate from transplant doses**
  The doses that suppress immunity differ from the low, intermittent doses studied for ageing.
- **Watch metabolic markers on a rapalog**
  Rising glucose or triglycerides may signal mTORC2 effects. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Weigh promising phase 2 data cautiously**
  This programme looked strong in phase 2 and still failed its phase 3 primary endpoint.
- **Use vaccine response as one biomarker of immune ageing**
  Ageing immune systems respond weakly to vaccines, so a better response is a measurable outcome.

#112 – Ned David, Ph.D.: How cellular senescence influences aging, and what we can do about it

Guest: Ned David
Date: 2020-07-08 · Duration: 2:15:33
URL: https://www.youtube.com/watch?v=BhayqoIg2Bc

KEYPOINTS

• David's framework: aging is flexible, nature has 'control knobs', and some can be turned

David, co-founder of Unity Biotechnology, points to similar creatures with very different lifespans. A hard clam lives about 40 years, while an ocean quahog has been aged at more than 500, roughly a 12-fold gap. Mammals range from shrews living under a year to bowhead whales, and rodents from field mice living two to three years to naked mole rats. Since the biochemistry is shared, he reasons that lifespan must be set by adjustable mechanisms.

• The first knobs discovered were insulin/IGF-1 signaling and calorie restriction

Cynthia Kenyon's daf-2 work in roughly one-millimeter C. elegans worms doubled lifespan by impairing one gene, a 'mind warp' when aging was seen as passive decay. David cautions that worms are a weak model; analogous receptor knockdowns in mice give far less longevity. Clive McCay at Cornell first extended rodent life with calorie restriction in the 1930s. David believes rapamycin and calorie restriction work through the same knob, mTOR.

• Other candidate knobs include young blood, mitochondria and the methylation clock

Experiments joining young and old animals date to the 1970s, which David notes is 'not exactly an optimal way to live.' He calls the methylation clock an area of intense debate. He uses the analogy of a vinyl LP, whose grooves wear down with each play, for how living itself might degrade the epigenetic record.

• Senescence is an anti-cancer emergency brake you don't want to remove

Mice engineered so they can't make senescent cells are born normal but are full of tumors before reproductive age. Unity's approach leaves the brake alone and clears cells only after they have permanently stopped dividing. Even in a single dish of identical irradiated cells, some die and about 99% of survivors become senescent, and nobody knows why cells choose one fate or the other.

• The damage comes from what senescent cells secrete

Senescent cells are only a small minority of cells, yet they can harm their neighbors through an inflammatory secretory profile, known as SASP, that co-founder Judy Campisi described in 2008. Campisi also found the first in-vivo marker of senescence around 1995. Leonard Hayflick overturned the dogma that cells divide forever in 1961, after earlier cultures had been contaminated by fresh cells in their feed.

• The company rested on four questions answered in parallel

The questions were: do senescent cells drive natural aging, can clearing them reverse a modeled human disease, can drugs selectively kill them, and will it work in humans. The 2011 Mayo Clinic paper from Jan van Deursen's lab got David to meet within 72 hours. A five-year natural-aging study published in 2016 was 'the trigger' to go public about Unity's work.

• Osteoarthritis became the first target

David calls osteoarthritis 'the primary reason it hurts to be old.' He says off-the-shelf pain models are irrelevant, so Unity used Jennifer Elisseeff's ACL-transection model at Johns Hopkins. Clearing senescent cells, genetically or with drug, reduced pain and regenerated cartilage in mice. In humans, senescent cells hover around 1–2% even in osteoarthritic knees, but their number scaled with disease and pain.

• Phase 1 knee data were striking but small

The trial enrolled 48 patients, randomized 3:1 to drug or placebo across six dose levels of about six patients each, with a single injection followed for three months. Pain fell in a dose-dependent way and hadn't returned at three months. At the top dose, pain dropped from about 6.2 to just over 1 on a 0–10 scale, mostly within two weeks. David stresses the small numbers and the large placebo effect seen with knee injections, and warns against comparing results across trials.

• Clearing senescent cells delayed cancer onset rather than changing its prevalence

In mice cleared from midlife until death, about 85% still died of lymphoma, but it appeared roughly 30% later in life, matching about a 30% lifespan extension. David calls this a phase shift of chronic disease and admits nobody knows why. The same mice kept 41% more intervertebral disc volume.

EXAMPLES

• Showing Hayflick the mice

David met Leonard Hayflick by chance at the Portland airport. He showed him photos of sibling mice with and without senescent cells, the phenomenon Hayflick had first described decades earlier, and watched him take it in.

• Lab mix-ups still happen

About a year before this conversation, Unity ordered what it thought were mouse cells from a cell bank. They turned out to be rat cells, which is why they weren't behaving properly. David cites it as a reminder of how the pre-Hayflick error could happen.

• The Phase 2 design

The study followed patients for 24 weeks, tested placebo plus 0.5, 2 and 4 mg doses with 45 patients per arm instead of six, and added MRI and X-ray to see whether pain relief comes with structural change.

• Kythera and Kybella

At David's earlier company, one of four clinical candidates worked: a molecule that makes fat cells burst. It became Kybella, for under-chin fat, and Allergan acquired the company. David says that experience taught him dispassionate decisions about drug-development risk.

OTHER RELEVANT

• Next frontiers: the eye, metabolism and the brain

Dry macular degeneration is about eight times as common as wet and has no treatment; only about one in eight macular degeneration patients has the treatable wet form. Unity planned injections into the eye, as with anti-VEGF drugs, using a different molecule than for knees, because senescent cells in different tissues have 'different Achilles heels.' Senescent astrocytes and microglia rise with age, and David finds it hard to imagine senescence plays no role in cognitive decline.

• Treat health span, not lifespan, as the realistic endpoint

Mortality is impractical to measure in trials, so diseases like osteoarthritis offer a path to approval while longevity effects are studied in animals.

• David's career advice

Slow down, because you have your whole life. Build around a single beautiful idea that gives you goosebumps. He compares an experiment finally working after 18–24 months to love for one's kids. And learn from people who are better and more patient than you.

#103 – Looking back on the first 99 episodes: Strong Convictions, Loosely Held

Date: 2020-07-08 · Duration: 1:17:22
URL: https://www.youtube.com/watch?v=CdfHFhpJqyc

KEYPOINTS

• 'Strong convictions, loosely held' means trying to shoot down your own hypotheses

For episode 100, Bob Kaplan interviews Attia about which of his views have changed since the podcast began in mid-2018. Kaplan quotes a blog by Richard Feinman, the SUNY biochemist (not the physicist Feynman), recounting a colleague's description of science: make a hypothesis, then try to shoot yourself down. Changing your mind is 'a feature, not a bug'.

• Attia stopped taking metformin

He had taken it since about 2011 for its possible longevity benefits, though few patients in his practice took it. In December 2018, when he started Zone 2 training and checking lactate again, his resting and low-effort lactate was surprisingly high. He concluded that metformin, a weak mitochondrial toxin, was probably blunting his mitochondrial output. He stopped, then spent months experimenting on and off it.

• Metformin's effect on training is still unclear

Studies of metformin's effects on muscle mass and training adaptation exist but seem suboptimal, because they often skip functional measures. Attia would like a large study using lactate, Zone 2 efficiency and muscle mass as proxies for whether the drug blunts the benefits of exercise in people without diabetes.

• Rapamycin took him years to act on

His interest dates to about 2012, peaked with the December 2014 everolimus paper by Joan Mannick and Lloyd Klickstein, and grew through 2017 interviews with David Sabatini and Matt Kaeberlein. Unlike most drugs, rapamycin has no biomarker to show you're taking enough or too much, beyond side effects such as mouth sores. It took him about four years to settle on a dosing approach, which happened around autumn 2018.

• Zone 2 came back into his training

After he stopped time-trial cycling around late 2014 or early 2015, he dropped low-intensity aerobic work entirely, something endurance athletes get without trying, even swimmers training for short events. Now it's a central part of his week. He enjoys it because it isn't hard, and there has never been a day he didn't want to do it.

• He now sees deadlifts as hugely valuable for longevity, if done properly

Starting dynamic neuromuscular stabilisation (DNS) about 18 months earlier changed his approach. He lifts lighter than before. He's rarely had 400 lb on the trap bar in the past year, tops out around 350–375 lb, and goes much lighter for slow tempo work. He films every rep of every set and sends it to his coach, Beth Lewis. His warm-up checklist of about 10 exercises takes 10–15 minutes.

• No more baby aspirin for flights

He used to assume that aspirin's antiplatelet effect prevented deep vein thrombosis on long flights. On digging, he found little evidence that it does. The gold standard, heparin, is impractical because it has to be injected, so he found supplement alternatives such as one sold as 'Flite Tabs'.

• Some generic drugs may not be equivalent

His default through medical school was that generics are identical and brand names a scam. But he has seen patients switched from Crestor to generic rosuvastatin show no change in their labs after two months, despite adherence they had no reason to lie about. Katherine Eban's episode (#71) on generic drug manufacturing shifted his view; he calls it one of the 10 most important episodes.

• He would push omega-3 levels higher

Before Bill Harris's episode, Attia targeted a red-blood-cell omega-3 index of about 8–10%. Afterwards he felt 12–14% could be reached without side effects and with more benefit. He says clinical trial data on EPA and DHA are still unclear, including a setback in a recent EPA-plus-DHA trial.

• Omega-6 associations are confounded

Foods high in omega-6 polyunsaturated fat are often 'crap', which makes associations hard to interpret. He calls it a polarising topic worth a deep dive. It matters little for his own diet but has big public-health implications.

EXAMPLES

• Archery as practice in stillness

At 20 yards an archer is expected to hit something the size of a quarter. A perfect round is 60 shots in the X ring. He uses a shot trainer for 20–40 practice draws a day in hotel rooms.

• A 1.44 GPA

Attia admits to a 1.44 high-school GPA while focused on sport. He contrasts it with his daughter's new self-driven studying.

• Getting a dog

After years of resisting, the family got a dog. A month in, it was far more work than expected, mostly for his wife and daughter.

• Learning to say no

He used to say yes to everything. Inspired partly by Jason Fried and Ric Elias, he's much better at declining, while avoiding the opposite extreme. He notes that Charlie Munger and Warren Buffett keep almost empty schedules.

• Reluctant podcaster

When the idea was first floated in about 2014, he called it the worst idea he'd ever heard, fearing the workload and that he'd run out of guests after 50 episodes.

• Books

He has reread Ryan Holiday's 'Stillness Is the Key' three times and recommends Siddhartha Mukherjee's 'The Emperor of All Maladies' and 'The Laws of Medicine'. He jokes that when you're writing a book, reading great ones makes you want to quit

writing yours.

OTHER RELEVANT

- **Re-test your convictions**
  Look for the data that would prove you wrong, as he did with metformin. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Check that a drug is working**
  With measurable drugs like statins, recheck labs. If nothing changes, suspect the formulation, not just adherence.
- **Don't assume aspirin protects you on flights**
  The evidence for aspirin preventing flight-related DVT is weak. Discuss real risk factors with a doctor.
- **Practise technique deliberately**
  Film your lifts, use a warm-up checklist and favour quality over load. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

#70–David Sinclair, PhD: How cellular reprogramming could slow our aging clock, & the latest on NAD

Guest: David Sinclair
Date: 2020-01-14 · Duration: 2:10:15
URL: https://www.youtube.com/watch?v=IgosGWLVUrU

KEYPOINTS

• Sinclair's 'information theory of aging'

Sinclair, a Harvard geneticist, discussing his book Lifespan, borrows from Claude Shannon's 1940s work on preserving information in noisy communication. He proposes that aging is mainly a loss of epigenetic information, meaning which genes should be on or off in a cell, rather than a loss of the DNA sequence itself. His analogy: the genome is a DVD, and aging is scratches that stop it being read correctly.

• Sirtuins began as yeast 'silent information regulators'

SIR stands for silent information regulator. In yeast, the SIR2 gene responds to dietary restriction, heat and starvation. Adding an extra copy extended yeast lifespan by about 30%, an experiment done by then graduate student Matt Kaeberlein. These proteins keep certain genes silent but leave their posts to repair broken DNA. Sinclair argues repeated repair calls gradually scramble the cell's program, and aging yeast lose cellular identity and become sterile.

• Methylation is the deepest, most stable layer

Cells mark genes to stay silent for decades by attaching methyl groups to DNA. Sinclair describes histone modifications as more changeable layers above it. The pattern of methylation at a few hundred sites shifts predictably with age, and he says it is very hard to reverse; the only way he knows is the Yamanaka stem cell reprogramming factors.

• The Horvath clock measures how fast you're aging

UCLA mathematician Steve Horvath trained algorithms on methylation sites to estimate age, about 95% accurate for chronological age. Sinclair says the clock starts ticking from conception, runs faster with smoking and sedentary living, and is slowed by exercise and calorie restriction. Universal clocks now work across tissues in humans and, from a Harvard group, in mice.

• Partial reprogramming aims to restore youth without erasing identity

Fully turning on the Yamanaka factors can be dangerous: Juan Carlos Izpisua Belmonte's Salk lab showed it can cause tumors in mice or kill them within about two days. Sinclair's lab leaves out the fourth factor, MYC, a known cancer gene. It delivers the other three, OCT4, SOX2 and KLF4, in an adeno-associated virus that switches on with the antibiotic doxycycline.

• Reprogrammed mouse eyes regained vision

With Bruce Ksander's lab, Sinclair's team tested three models: a crushed optic nerve, raised eye pressure mimicking glaucoma, and naturally aged mice around 12 months old, which they compare to roughly 40-year-old humans. They report regenerated nerves in all three and restored vision in the glaucoma and old mice, measured by whether mice turn their heads to track moving lines. Treated retinal cells had a younger methylation age, with Horvath's help.

• Peter presses on whether boosters touch the deep clock

Sinclair says early data suggest rapamycin, NAD boosters and metformin have relatively little effect on the methylation clock and at best slow it, whereas reprogramming appears to reverse it. Peter wonders whether a week-long fast or pulsed rapamycin, which he takes, might shift it. The two imagine a future clock test read from interstitial fluid, much like today's continuous glucose monitors.

• NAD and the oral-precursor debate

Sirtuins need NAD as fuel, with resveratrol acting as the 'accelerator.' The body converts NR to NMN to NAD and keeps recycling it. Peter cites Joshua Rabinowitz's Princeton tracer study showing oral NR in mice was mostly converted in the liver, raising blood nicotinamide more than NR. A later human trial using 1,000 mg of NR raised muscle NAD but was not yet peer-reviewed. Sinclair suspects gut microbes strip nicotinamide off NR and NMN.

• The benefits may be greatest in the least healthy

Both men note a recurring pattern with metformin, resveratrol and NAD boosters: benefits are clearest in obese or sick mice and people. Peter worries that the health-obsessed people most likely to take these molecules may benefit least. Sinclair agrees the human evidence is incomplete.

EXAMPLES

• Smoking history written in DNA

Peter recalls Sinclair's story that the methylation clock predicted how much people had smoked better than their own recollection. It matched medical records rather than self-reports.

• A small ALS trial

A tiny study of high-dose NR plus pterostilbene (1,000 mg and 200 mg) in ALS patients reported better forced vital capacity than placebo. It had many dropouts and no hard endpoints. Peter suggests effects may show up mainly in severely stressed patients.

• The resveratrol mechanism dispute

Sinclair says a mutation in SIRT1, a 'stiff elbow,' blocks resveratrol's activation. He says repeating his 2006 high-fat-diet mouse study in mutant mice showed resveratrol's benefit depends on SIRT1. He says he takes a gram each morning with homemade yogurt.

• First human target: the eye

The eye is a protected organ where roughly half of optic nerve cells can be reached by the virus. Sinclair hoped to start a glaucoma trial within about 18 months. He suggests the prostate as another possible target, saying about 40% of 50-year-old men already have prostate cancer, though most of it won't kill them.

OTHER RELEVANT

- **Pulse your stressors**

  Sinclair skips metformin on days he exercises because it may blunt mitochondrial gains, taking it when traveling instead, and only when his stomach tolerates it. He avoids rapamycin around training and stops supplements during fasts longer than a day, admitting there is no direct evidence behind this.

- **Pterostilbene isn't proven superior**

  Pterostilbene is a methylated relative of resveratrol. Sinclair says he has seen no data supporting marketing claims that it beats resveratrol, and nobody knows whether the two match milligram for milligram.

- **Next-generation NAD boosters**

  His lab's NAD prodrugs are designed to absorb better, resist gut bacteria and stay stable. The most advanced was in a phase 1 study in healthy volunteers at Brigham and Women's Hospital.

#66 – Vamsi Mootha, MD: Aging, T2D, cancer, dementia, Parkinson’s—do all roads lead to mitochondria?

Guest: Vamsi Mootha
Date: 2020-01-13 · Duration: 2:27:53
URL: https://www.youtube.com/watch?v=k3ZPCyfKvYo

KEYPOINTS

• Mitochondria are domesticated bacteria with a stripped-down genome

Over evolution, about a thousand genes from the original bacterium were lost or moved to the nucleus. The human mitochondrial genome is now about 16,000 base pairs and encodes 13 proteins, two ribosomal RNAs and 22 tRNAs. Mootha notes the malaria parasite's mitochondria encode only three proteins, while Giardia ('beaver fever') has lost its mitochondrial DNA altogether.

• Mitochondrial disease isn't just 'maternal'

There are about 250 distinct syndromes caused by mutations in mitochondrial DNA. But most of the roughly 1,000 proteins that mitochondria need are encoded in the nucleus, so many disorders are recessive nuclear mutations rather than maternally inherited. Mootha says clinical training overemphasised maternal inheritance because those cases were easiest to recognise.

• Why mitochondrial DNA comes from your mother

An unfertilized egg holds about half a million copies of mitochondrial DNA, more than any other cell, while a sperm has a few hundred at best. Beyond being outnumbered, sperm mitochondria are tagged with ubiquitin and actively destroyed after fertilization.

• Mitochondria turn over within days

In non-dividing tissues such as muscle and neurons, Mootha estimates the half-life of mitochondrial components at a few days, so the body is constantly building and recycling them. Counting individual mitochondria is ambiguous because they continually fuse and divide, so copies of mitochondrial DNA are the better unit.

• NAD is both an electron carrier and a consumable

NAD shuttles electrons in the electron transport chain to power ATP production, but sirtuins and DNA-damage enzymes also use it up. That's why NAD can fall quickly in cells with damaged DNA. Muscle biopsies show NAD, mitochondrial content and VO2 max all declining with age, but Mootha says the open question is whether sick mitochondria cause tissue aging or simply accompany it.

• Too much oxygen, not just too little ATP, may drive some mitochondrial disease

The textbook view is an energy shortage, but Mootha's lab finds that glycolysis largely defends ATP at rest. Because mitochondria consume most of the oxygen we breathe, broken ones leave unused oxygen in tissues, which can be toxic. Patients often show unusually high oxygen in venous blood.

• Reduced mitochondrial function shows up before type 2 diabetes

Papers in 2003–04 from Mootha, Leif Groop, David Altshuler, Ron Kahn, Gerald Shulman and others found that healthy people with a family history of diabetes had slightly lower expression across the whole set of mitochondrial genes, fewer mitochondria and lower VO2 max. Fifteen years later, whether this causes diabetes or reflects some upstream factor remains unresolved. Mootha's team was attempting to answer it with Mendelian randomization.

• Partly blocking the electron transport chain can extend life in worms

RNAi screens by Gary Ruvkun and Cynthia Kenyon found electron-transport genes among those whose disruption lengthened worm lifespan, and also among those that shortened it. One explanation is dose: gentle inhibition triggers protective responses, while severe loss kills. Mootha suggests metformin, a complex I inhibitor, may work through such a mild hit.

• Exercise is the best known way to renew mitochondria

Mootha says no drug yet rejuvenates mitochondria directly. Exercise both clears damaged ones and builds new ones. Both he and Attia are skeptical of 'exercise in a pill' headlines; Attia points to crude news coverage of irisin.

EXAMPLES

• Hypoxia rescued mice with Leigh syndrome

Mice lacking a complex I subunit look normal at birth, sicken around days 30–35 and meet euthanasia criteria by day 55–60. Raised at 11% oxygen (similar to 18,000 feet, about Everest base camp) instead of 21%, they lived to a median of about one year and looked so healthy that the team suspected a genotyping error. Mootha stresses this is in mice only and works in some models of mitochondrial disease, not all.

• Attia's metformin and lactate experiment

Testing himself on a bike in 5–10-watt steps, Attia found his resting lactate rose from below 1 mmol/L to between 1 and 2 on metformin, about double, with higher lactate during exercise too, confirmed using two meters. He calls it an N-of-1 observation consistent with complex I inhibition diverting pyruvate to lactate. Mootha offered to run fuller metabolite profiles on and off the drug.

• A textbook on a cousin's bookshelf

Stranded at his dad's cousin's home in Somerville on a Friday night when the subway shut down during his miserable first year of medical school, Mootha found a mitochondrial biology textbook, read about 100 pages that night and decided on his life's work.

• Hyperbaric oxygen for selected cancers

Flooding tumours that have weak mitochondria with oxygen might harm them, and Mootha has an oncologist in his lab exploring this. Past results with hyperbaric oxygen in cancer have been mixed. He expects any benefit to be limited to a rare subset of tumours with mitochondrial defects, identified by sequencing rather than by tissue type.

OTHER RELEVANT

- **Don't read too much into supplement hype**
  Mootha's distinction between correlation and causation applies to NAD boosters: falling NAD tracks aging, but replacing it hasn't been shown to reverse tissue decline in humans.
- **Metformin may blunt exercise adaptations**
  Attia's lactate data and the complex I mechanism raise the question of whether metformin interferes with exercise benefits in non-diabetics. Its benefits in diabetes and insulin resistance are well supported, while longevity benefits in healthy people are the open question Nir Barzilai's TAME trial aims to answer.
- **Low-oxygen therapy is still experimental**
  Mootha and Attia picture a future where families of children with Leigh syndrome might move to high altitude. For now it's an animal finding, as both of them emphasise, not a treatment to attempt.

#43–Alan Bauman, M.D.: The science of male and female hair restoration—how to protect & restore hair

Guest: Alan Bauman
Date: 2020-01-08 · Duration: 1:55:56
URL: https://www.youtube.com/watch?v=M5B8tNCXEy4

KEYPOINTS

• Hair loss is very common and usually under-treated

Bauman, a hair restoration surgeon who says he has treated more than 20,000 patients, puts the US total near 100 million: about 80 million men and 46 million women. His rule of thumb for men is roughly 20% with visible loss in their 20s, 30% in their 30s and 40% in their 40s. Because about half the hair can be gone before the eye notices, loss can start any time after puberty without being seen.

• 'Premature' hair loss is a meaningless term

Bauman compares hair loss to greying: its timing is genetically set along a spectrum, and 'premature' is in the eye of the beholder. Pattern loss can skip siblings and generations. He describes families where a grandfather, father and sons all come in together.

• DHT drives male pattern loss, and finasteride works for most men

In genetically susceptible men, dihydrotestosterone 'kills' follicles. Finasteride, at about 1 mg a day, gives roughly a 90% chance of looking the same or better over about five years, the usual length of a clinical trial. Dutasteride blocks both pathways to DHT more strongly, but some DHT still gets through either way. Bauman calls finasteride's side-effect rate very low but acknowledges that some men get sexual side effects.

• The finasteride prostate-cancer signal may be partly a biopsy artefact

Attia calls the prostate data confusing: lower rates of prostate cancer but possibly higher grade when it occurs. Bauman passes on an explanation from urologists. Finasteride shrinks normal prostate tissue, and everyone in a trial is biopsied, so high-grade cancer may be easier to find. He presents this as what was explained to hair surgeons, not settled science.

• Finasteride was designed for hair; minoxidil was found by accident

Merck knew from the start that finasteride would be a hair-loss drug. It won approval first for the prostate, as Proscar at 5 mg, then for hair loss, as Propecia at 1 mg, in 1998. Minoxidil was a 1970s blood-pressure pill whose hair growth was noticed as a side effect. Rogaine's FDA approval began clearing useless tonics off the market.

• Minoxidil keeps follicles in the growing phase

In a healthy scalp, about 84–85% of follicles are in anagen, the growth phase. In pattern loss, more are resting and anagen shortens, producing short, spiky, miniaturised hairs visible along a part. Minoxidil wakes resting follicles and prolongs anagen, and the longer anagen lasts, the thicker the fibre becomes. It won't restore a receded hairline but can slow further loss.

• Micro-inflammation at the follicle matters

Bauman took part in a University of Miami study using donated follicles that found inflammasome activity around them. That helps explain the anti-inflammatory ingredient in his compounded minoxidil and the interest in scalp health. When he examines the scalp, he often finds treatable problems such as fungal infection.

• Women's hair loss isn't just about DHT

Pregnancy keeps more follicles in growth, which is why hair thickens and then sheds after birth. Thinning a decade or more after the last child can reflect androgen sensitivity even when DHT is low. Oral finasteride works in about 50% of postmenopausal women but is used off-label only after childbearing years, because DHT is essential to a developing male fetus. It isn't FDA approved for women.

• Donor dominance is why transplants last

Follicles from the sides and back of the scalp are almost immune to DHT, and transplants rely on the theory that they keep this resistance on top of the head. Bauman notes only very limited evidence against it. Transplanted hair doesn't stop the native hair from thinning, so patients who don't protect existing hair 'face a much tougher battle'.

• The main risk of a transplant is an unhappy patient

Bleeding stops like a shaving nick, and the worst infection is usually a pimple-like ingrown hair. Roughly one in 20–30 patients needs more wound care. The real risk is mismatched expectations: promising a 10 out of 10 when the outcome will be a five. Bauman says that after 8,000 surgeries he can show patients the range of results seen in similar cases.

EXAMPLES

• Bauman's compounded minoxidil, 82M

Instead of off-the-shelf foams, his prescription formula adds 0.025% tretinoin, which he says improves penetration and growth, plus 'a whiff' of the steroid fluocinolone. The bottle's tip is applied directly to a parted scalp, which takes 90 seconds twice a day. He says once-daily over-the-counter use rarely does much.

• Laser caps that fit under a baseball cap

Low-level laser therapy targets cytochrome c oxidase in the follicle. Attia notes the same idea is being studied in Alzheimer's. Old laser combs had to be moved around the head; caps now sit under a baseball cap with a battery pack, on schedules like 20 minutes every other day. Bauman says they have no side effects and are useful for people, like college students, who won't apply minoxidil twice a day.

• PRP with measured platelet counts

Platelet-rich plasma comes from the patient's own centrifuged blood. Baseline platelet counts vary, from around 150,000 to 250,000 per microliter, so Bauman counts platelets before and after processing in an in-office Beckman Coulter counter. After about 4,000 treatments he emphasises 'monocyte-rich' PRP. He injects with a 27-gauge needle under a full local block, with optional nitrous oxide. Attia notes PRP's evidence is mixed in orthopaedics and that platelet count is a crude measure.

- **From ear-to-ear strips to 1 mm punches**

  Older strip harvests removed strips 10–20 cm long and 1 cm wide, and technicians dissected 2,000–3,000 grafts under microscopes, often leaving wide scars. Follicular unit extraction uses a punch under 1 mm. The holes close about 50% in 24 hours and need no stitches. Bauman designed an early hand-turned instrument for it, though he says many infomercial clinics still harvest strips.

- **Big cases and beard donors**

  Large procedures now run about 3,500–4,000 grafts over two consecutive days rather than one marathon session. Beard hair can be harvested to repair old strip scars. Bauman's father, who was totally bald, has had almost 8,000 grafts.

OTHER RELEVANT

- **Get measured early if hair loss runs in your family**

  Bauman uses a trichometer to measure hair mass index, combining density and diameter, in permanent zones compared with thinning ones. Parents often bring teenagers in before college.

- **Check your medications**

  Bauman lists blood-pressure, cholesterol and mood medications as the top three that can affect hair quality, often noticeable from when they were started.

- **See someone who looks at your scalp**

  He hears from many patients who had blood tests from several doctors, but nobody examined their scalp or offered more than a bottle of Rogaine.

- **Condition the hair fibre, treat the scalp**

  Heat styling and chemical products weaken hair; conditioner belongs on the fibre. Conditions like psoriasis need real treatment, not just a supermarket shampoo.

#35 – Nir Barzilai, M.D.: How to tame aging

Guest: Nir Barzilai
Date: 2020-01-07 · Duration: 2:47:45
URL: https://www.youtube.com/watch?v=A80l3o8cz7k

KEYPOINTS

• Nir was studying metformin's mechanism in 1987—before US approval.
As an endocrinology/aging researcher he worked the drug's biology early, then watched interest fade until the geroscience wave revived it. That long arc is why he treats metformin as both an old diabetes tool and a candidate aging intervention, not a Twitter novelty. That early unfinished business with metformin is emotional fuel for TAME as much as scientific rationale. Few clinicians pairing bedside endocrinology with centenarian genomics bring that specific scar tissue to the metformin debate.

• Insulin resistance may be a stress response, not only a villain.
Animal work he discusses complicates the cartoon: manipulating visceral fat and watching diabetes onset in rodents suggested resistance can be protective modulation under some conditions. Clinically he still fights hyperglycemia; intellectually he wants finer definitions than 'IR bad, always.' Peter presses him on clinical translation: nuance about IR as modulator must not become an excuse to ignore diabetes risk.

• TAME (Targeting Aging with Metformin) aims to treat aging as an indication.
Because metformin is pennies, pharma will not fund the usual path—Nir jokes his yearly supply costs pocket change. TAME is designed to show delayed onset of a basket of age-related diseases, creating a regulatory path for aging itself rather than one disease at a time. Regulatory creativity—aging as indication—is half the scientific project. Success would unlock a playbook for testing other aging drugs without forcing every compound into a single-disease silo.

• Existing human signals: DPP, UKPDS, and observational dementia/cancer hints.
Diabetes Prevention Program evidence for preventing diabetes, UKPDS cardiovascular signals, and emerging Alzheimer/cancer literature are why he thinks the prior for a broader aging effect is not crazy—even while demanding a proper trial. He is explicit that hints are not TAME; they are why TAME is ethical to run.

• Centenarians get a ~20–30 year 'bonus' and still die of the same diseases.
They are not immortal; they postpone heart disease, cancer, and Alzheimer's. End-of-life costs in his cited comparisons can be lower for those dying after 100 than at 70—compression of morbidity as an economic and human argument. Families of centenarians often show the delay pattern across siblings, pointing beyond pure luck. That pattern—same exits, later tickets—is the healthspan definition Nir wants policymakers to fund.

• Centenarian genetics are not a 'perfect genome.'
When his group checked ClinVar-style pathogenic mutation lists, centenarians were not mutation-free; many carried plenty. The gift looks more like protective variants and buffering (including pathways around IGF/GH and lipid genes such as CETP patterns he studies) than absence of all risk alleles. CETP VV and related lipid genetics appear in his longevity cohorts as clues, not consumer kit destiny.

• IGF/GH axis cuts both ways for aging and disease.
Too much growth signaling links to certain chronic diseases; too little harms resilience. Nir and Peter dig into whether boosting HGH for lifestyle reasons is wise (generally skeptical) versus understanding naturally low-IGF protective genotypes in long-lived kindreds. Peter's clinical instinct against casual HGH aligns with Nir's read of the aging biology.

• NAD precursors (NR/NMN) get curiosity without blank checks.
They discuss the hype cycle around NAD boosters frankly: promising mechanistic stories, thinner long-term human outcome data than the marketing. Metformin, for Nir, remains the nearer-term pragmatic test. Both prefer waiting for clearer trials over stacking unproven NAD protocols on healthy middle age.

• Max human lifespan arguments sit near ~115–122 with statistical caveats.
Dying before 80 on average leaves decades of theoretical healthspan on the table. TAME's ambition is capturing a slice of that gap with a safe, cheap drug already used by millions. Even a five-year delay in multimorbidity would be civilization-scale if it generalized.

• Both men hunt their own blind spots out loud.
Peter worries about over-interpreting rodent metformin data; Nir worries about under-interpreting converging human signals while waiting for perfect evidence. The episode models adversarial collaboration more than guru monologue. Listeners hear two experts willing to say 'I might be wrong' in real time—rare and useful.

EXAMPLES

• 1987 metformin mechanism work
Pre-approval research that later informed why a diabetes drug might touch aging biology broadly. Few guests can claim continuous metformin curiosity across that many decades.

• TAME's economic irony
A ~10-cent/day drug cannot attract conventional blockbuster ROI—hence academic/consortium trial design. If the trial works, it becomes a template for other gerotherapeutics regulators currently struggle to classify.

• Centenarians vs ClinVar mutations
Hypothesis of 'perfect genome' failed; protective biology > mutation absence. Protective variants plus resilient IGF/insulin handling beat fantasy flawless DNA. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

• Morbidity compression cost sketch
Last-two-years costs lower after death at 100+ vs 70 in the comparisons he cites—aging delay as system savings. Healthspan arguments gain political force when they also shrink late-life spending.

• Sprague Dawley cancer-dominant deaths

Rodent reminders that extending life still ends in disease—timing and multimorbidity are the targets. Species-specific causes of death keep everyone honest about translation limits.

OTHER RELEVANT

- **Do not self-start metformin casually without medical context.**
  Nir's enthusiasm is trial-shaped; GI side effects, B12, and contraindication checks still matter. Ask a physician who knows your kidneys, B12, and GI history before experimenting.
- **Watch TAME-style endpoints, not Instagram biomarkers alone.**
  Delayed disease onset across a basket beats a single lab vanity metric. Follow disease-onset baskets and disability-free years, not only fasting glucose.
- **Be skeptical of lifestyle HGH for anti-aging.**
  Growth-axis genetics of centenarians "` indication to inject GH at 45. Skip lifestyle GH clinics selling youth; the biology is not a nightclub flyer.
- **Treat NAD hype as hypothesis-generating.**
  Mechanistic plausibility is not a substitute for hard clinical outcomes. File NAD under 'interesting,' not under 'settled longevity stack.' The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

#36 – Eric Chehab, M.D.: Extending healthspan and preserving quality of life

Guest: Eric Chehab
Date: 2020-01-07 · Duration: 2:38:45
URL: https://www.youtube.com/watch?v=CUcEAgdlXhA

KEYPOINTS

• Orthopedics is a healthspan specialty more than a lifespan specialty.
Eric Chehab—Peter's Stanford med-school friend, HSS-trained sports surgeon, New York Giants fellow, now University of Chicago faculty—spends his days restoring strength, mobility, and freedom from pain. When those collapse, many patients stop caring about another year of life; quality of daily living becomes the whole ballgame.

• Loaded bad form is a leading author of gym-related joint pain.
They walk through knee pain from incorrect mechanics under load, shoulders irritated by poorly progressed overhead pressing, and the elbow/wrist/Achilles problems that show up when volume outruns tissue capacity. Early technique coaching is prevention disguised as performance work. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

• Not all joint pain maps cleanly to the MRI finding.
People present with 'knee pain' or 'shoulder pain' whose imaging shows age-typical wear that may not be the pain generator. Eric pushes matching history, exam, and imaging before leaping to the OR—especially for meniscus tears where physical therapy often rivals or beats arthroscopy for many presentations.

• Meniscus surgery sits in a real evidence controversy.
For degenerative tears in middle age, trials have cooled enthusiasm for routine scope-and-trim. Traumatic tears in younger athletes still play by different rules. Eric helps listeners separate Instagram surgery culture from indication-driven care. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

• Rotator-cuff logic also shows up around the hip abductors.
Hip abductor tendons can fail in cuff-like patterns, but the hip's weight-bearing congruence changes the stakes. Understanding those analogies helps patients interpret why some 'bursitis' stories are actually tendon stories. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

• Lower-back pain almost always starts with PT, not surgery.
Eric's rule of thumb aligns with Peter's: for axial low-back pain, non-operative care is the default. Surgery earns its keep in clear neurologic compression or instability—not as a first response to a bad week of stiffness. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

• Mentorship from Russ Warren shaped his reconstruction philosophy.
Warren, a godfather of sports medicine and early ACL/arthroscopy pioneer with a legendary paper count, modeled meticulous indication-setting at HSS. Fellowship time with the Giants added the return-to-play pressure cooker on top of that academic base. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

• Tissue capacity must rise with ambition.
Masters athletes who add heavy overhead work or sudden running volume without progressive loading buy tendinopathy. Eric's prevention sermon is boring on purpose: gradual exposure, deloads, and honest appraisal of recovery age. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

• Pain that steals ADLs should trigger earlier specialty care.
Waiting until stairs, sleep, or work tasks fail makes rehab harder. Healthspan framing means treating mobility loss as urgently as many people treat a scary lab value. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

• Friendship plus shared training history keeps the episode practical.
Peter and Eric translate OR wisdom into gym cues listeners can use Monday: scapular control, knee tracking, and when to stop 'pushing through' a warning twinge. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

EXAMPLES

• HSS + Giants fellowship path
Hospital for Special Surgery residency culture plus pro-football coverage: high-volume ACL and shoulder decision-making under return-to-sport deadlines. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

• Meniscus trial humility
Degenerative tear evidence that made 'always scope it' outdated—PT-first for many middle-aged patients. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

• Overhead press shoulder flare
Classic lifter pattern Eric and Peter use to teach progression and scapular mechanics. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

• Hip abductor as 'cuff' analogue
Helps patients understand lateral hip pain beyond the vague bursitis label. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

- **ADL collapse as the true endpoint**
  When pain removes independence, lifespan talk loses relevance—Eric's north star metric. Peter and the guest sit with the nuance rather than flattening it into a slogan, which is why the episode rewards a full listen-through of the key points.

OTHER RELEVANT

- **Film your lifts before your joints file a complaint.**
  Catch valgus knees and shrugging presses early; form is cheaper than MRI.
- **Ask whether the MRI lesion explains this pain.**
  Age-related findings are common; treat the person, not every bright spot on the scan.
- **Default to PT for back and many meniscus presentations.**
  Earn surgery with clear mechanical indications, not impatience.
- **Progress load slower than your ego wants after 40.**
  Tissue adaptation lags ambition; deloads are part of the program.

#27 – David Sinclair, Ph.D.: Slowing aging – sirtuins, NAD, and the epigenetics of aging

Guest: David Sinclair
Date: 2020-01-06 · Duration: 1:41:32
URL: https://www.youtube.com/watch?v=edrIEC0kJv8

KEYPOINTS

• Sirtuins came from an unbiased genetic hunt in yeast

In Lenny Guarente's MIT lab, gene screens for yeast lifespan turned up SIR genes ('silent information regulators'), not the DNA-repair or antioxidant genes the field expected. Sir2, which has counterparts in mammals, controls gene silencing. Sinclair notes that at the time aging was blamed mainly on DNA damage and free radicals, so a gene-silencing protein was a surprise.

• Sirtuins move to repair damage and neglect their usual jobs

Sinclair and student Kevin Mills stained the proteins and saw them relocate to the nucleolus, home of the ribosomal DNA, during normal aging and during an accelerated form of aging. His lab and others then showed that sirtuins were both necessary and sufficient to mimic calorie restriction in yeast and mammals. Knocking them out weakens the lifespan benefit, though Sinclair concedes that intense stress can bypass them in yeast.

• NAD fuels sirtuins, and nicotinamide brakes them

Sirtuins consume NAD and release nicotinamide (a form of vitamin B3). When his first student, Kevin Bitterman, fed yeast nicotinamide expecting activation, he got inhibition. Sinclair explains it as a negative feedback pocket in the enzyme that senses its own by-product, and says he wouldn't recommend very high doses of nicotinamide. Labs worldwide now use it as a sirtuin inhibitor.

• Calorie restriction switches on NAD recycling

PNC1, an NAD-salvage gene previously studied in tuberculosis, was among the most strongly upregulated genes in calorie-restricted yeast. That connected nutrient stress to higher sirtuin activity through NAD.

• Resveratrol was a proof-of-concept activator, not a drug

In 2003, Konrad Howitz at Biomol screened compounds and found plant molecules that appeared to activate human SIRT1. The two labs spent about six months trying to disprove it, because true allosteric activators are rare. What convinced Sinclair was that the molecules extended yeast lifespan only when the sirtuin gene was present. Even so, he calls resveratrol 'a terrible molecule' because it dissolves so poorly.

• Mouse results depended on diet and absorption

In his 2006 study, middle-aged mice on a high-fat, high-sugar 'Western' diet given resveratrol (about 200 mg/kg/day, by his recollection) lived roughly 20–25% longer than equally fed controls. The NIA's Interventions Testing Program later found no lifespan extension with resveratrol mixed into standard chow, which Sinclair says matches his own data and reflects absorption. He says fat improved blood levels in his studies, so he takes it with oil or yogurt.

• His personal regimen comes with explicit uncertainty

Sinclair takes about a gram of resveratrol, reasoning that if it doesn't work at a gram it won't work at more. He also takes metformin at a low dose because the pathways overlap and stacking compounds is 'unknown territory', plus NMN. He doubts resveratrol will add even five years to his life, but believes it may delay cardiovascular disease.

• Aging as loss of analog information

Sinclair previewed an unpublished 'unifying theory'. DNA is digital and stays largely intact in old animals, he says, while the epigenetic pattern of which genes are switched on is analog and degrades like a scratched CD. Using Waddington's 1950s landscape, he describes cells as marbles jostled out of their valleys until neurons and liver cells lose their identity. His lab was writing up experiments in which manipulating the epigenome produces hallmarks of aging.

• Old eggs may suffer from low NAD

Sinclair links egg aneuploidy to faulty spindles. He describes a kinase that controls spindle quality, regulated by the NAD-dependent sirtuin SIRT2, and says giving NAD precursors to older mice produced healthier, more numerous eggs. Whether this applies to sperm is untested. This is mouse work, not a human fertility treatment.

EXAMPLES

• The 10-gram resveratrol trials

Worried about poor absorption, clinical researchers dosed people at about 10 grams a day. A couple of late-stage cancer patients developed kidney failure, which Sinclair notes happens anyway in such patients, but the company decided it wasn't worth pursuing for a would-be blockbuster.

• Starting at the equivalent of age 70

Sinclair says unpublished work from his lab extends mouse lifespan even when treatment begins after 600 days, roughly 70% of the way through life, and hinted that NMN given in drinking water to normal mice was involved.

• The 5,000-person trial he'd fund

With unlimited money, Sinclair would give metformin, rapalogs or NAD precursors to about 5,000 people in their 70s for three to four years and look for a change in the mortality hazard ratio. He puts the cost in the tens of millions against potential savings in the trillions. Attia compares the design to Nir Barzilai's metformin (TAME) trial, which focuses more on healthspan.

• A grandmother who never lied

Sinclair traces his focus on mortality to his grandmother Vera (who insisted on being called by her first name) answering his childhood question honestly: everyone he loved, his cat and he himself would die. He notes that children typically grasp death between four and seven, then bury the thought until around 50.

OTHER RELEVANT

- **Products using Sinclair's name aren't endorsed by him**

  He says nothing sold over the counter carries his name with his or Harvard's permission, and that he has sent many cease-and-desist letters. Be skeptical of supplements marketed with his name.

- **Don't megadose B3 to boost NAD**

  Because nicotinamide inhibits sirtuins through feedback, Sinclair advises against very high doses. Precursors like NR and NMN, he says, are still early, and we don't yet know which tissues take them up preferentially.

- **Introduce compounds one at a time**

  Following Sinclair's caution about overlapping pathways, if you combine metformin, resveratrol or NAD precursors with your doctor's oversight, start low and add one thing at a time rather than stacking full doses.

#13 – Brett Kotlus, M.D.: How to look younger while we live longer

Guest: Brett Kotlus
Date: 2019-12-23 · Duration: 1:48:51
URL: https://www.youtube.com/watch?v=4hF6_XxgTs4

KEYPOINTS

• Facial aging combines sun damage, thinning skin and shifting volume

Kotlus, an oculoplastic and cosmetic surgeon, says years of sun exposure cause solar elastosis. Collagen and elastin fall, the skin gets thinner, and small blood vessels (telangiectasias) and brown spots appear. Meanwhile the face loses volume, sometimes in the wrong places. In his practice, darker skin types and many Asian patients tend to age better. He attributes this to denser connective tissue and the UV protection pigment provides, while stressing that they still need sunscreen.

• Kotlus suspects UV exposure slowly destroys facial fat, but calls it a hypothesis

His reasoning is by analogy. Focused heat and laser devices are known to destroy fat cells, so he believes decades of UV may do something similar to facial fat. As supporting observation, he points to lifelong sun-avoiders with 'porcelain skin' who have fewer wrinkles and younger-looking faces. He frames it as his own belief, not established science.

• Looking 'done' comes from over-enlarging or over-pulling natural shapes

A natural face needs shadows and movement. He gives the analogy that you can't have light without dark. Overfilled lips lose the Cupid's bow and the 'two pillows' of the lower lip and turn into a 'sausage'. Over-tight facelifts create the windswept look. His rough guideline is to aim for looking about seven to ten years younger, because 'there's no amount of money' that makes someone look naturally 30 years younger.

• Social drift and 'provider shopping' push people too far

Kotlus describes an 'Instagram effect': filtered and augmented faces start to look normal, peer groups escalate together, and some patients find a new injector when one says stop. Peter adds that he only sees the badly done cases, the numerator, and not the denominator of people whose work goes unnoticed.

• Hyaluronic acid fillers are biocompatible and reversible, but lips swell at first

Hyaluronic acid already exists in skin, allergic reactions are generally absent, and an enzyme can dissolve it if something looks wrong. The gels attract water, so lips look oversized for about two to three days. He says almost every first-timer then admits they 'sort of missed' the swelling and wants more next time. Lip filler lasts about six to eight months; under-eye filler lasts one to two years and sometimes four to five.

• Bad Botox is usually too much in the forehead

The frontalis is the only muscle that raises the eyebrows. Heavily injecting it to erase horizontal lines leaves a shiny, frozen forehead and brows that actually drop, which he calls a giveaway at the Oscars. He says a better approach often targets the corrugator and procerus muscles between the brows that cause frowning. Modern technique uses smaller amounts spread more widely, and can lift mouth corners, reduce a gummy smile or open the eyes slightly.

• Start prevention before lines become etched

Kotlus emphasizes that nobody has to do any of this. For those who care, prevention comes first: sun avoidance from youth, and possibly neurotoxin before expression lines become permanent creases, for example if you see those lines on your parents.

• His three core skincare tools are sunscreen, a retinoid and topical vitamin C

Retinoids act at the gene-transcription level, boosting collagen and cell turnover. He calls them one of the few proven anti-aging treatments. Vitamin C is an antioxidant and a collagen cofactor, and it works better with vitamin E. Its caveat: if blood vitamin C is already high, skin may absorb topical C poorly. Evidence supports it for reversing existing sun damage more than for preventing it. He says some patients improve dramatically from this regimen alone, 'without touching them with a needle'.

• Some devices are operator-independent, but lasers and peels are not

For cryolipolysis such as CoolSculpting, or heat-based alternatives, the main point is to use an FDA-approved device rather than a knockoff. He says these typically reduce about 20% of subcutaneous fat over a course of treatment. Peels and resurfacing lasers depend heavily on the operator.

EXAMPLES

• Peter's forehead Botox misadventure

About six years earlier, a plastic surgeon friend gave Peter what felt like 'three thousand injections' into his forehead. He then couldn't raise his brows to keep sweat out of his eyes while cycling under a helmet. Kotlus uses this as the textbook frontalis mistake.

• Kotlus's cannula technique for under-eye hollows

Kotlus says under-eye hollows are his most frequent procedure. The tear trough shadow forms when cheek fat is lost while the eye fat pads enlarge, making people look tired. He enters through a single needle hole in the cheek with a blunt-tipped cannula, so no needles go under the eye. He places filler by picturing the anatomy he sees during blepharoplasty, and stresses that some hyaluronic fillers are the wrong stiffness or water-attraction for that area.

• SPF numbers and sunscreen types

SPF measures UVB (burning) only. SPF 15 means taking 15 times longer to redden, so 10 minutes becomes 150. He cites roughly 96% versus 98% protection for SPF 30 versus 50. He recommends broad-spectrum physical (zinc or titanium) sunscreen of at least SPF 30 and avoids octinoxate, while noting that dose-related harm is debated. Chemical filters convert UV to heat, which can worsen melasma.

• PRP: Kotlus offers it but finds it often oversold

Kotlus draws about 80 mL (ten 8 cc vials) and double-spins it. Methods vary widely, which muddies the research, and some providers inject platelet-poor plasma as 'PRP'. Peter tried scalp PRP for hair loss and was underwhelmed. Kotlus notes that DHT-driven hair loss continues regardless, so finasteride or dutasteride and minoxidil may be needed.

• Peel strength matters

A 10% TCA peel leaves skin slightly red. A 35% peel makes it come off 'like a snake'. Phenol peels require EKG monitoring for arrhythmias. Fractional erbium and CO2 lasers leave dots of untreated skin between treated areas to aid healing.

OTHER RELEVANT

• Retinoid how-to

Start with an over-the-counter retinol. If it dries the skin, use it every second or third day or wash it off after 10 minutes. Then move to prescription tretinoin at 0.025%, 0.05% or 0.1%; Kotlus uses 0.1% nightly. Apply it at night, including the upper eyelids to the lash line. He says the sun-sensitivity concern is mostly about the retinoid breaking down in light.

• Morning order of operations

Apply vitamin C serum, wait a couple of minutes until it's dry, then apply sunscreen; apply the retinoid at night. Most people under-apply sunscreen, so also wear a wide-brim hat and cover the chest and hands.

• Choose a provider, not a device

Kotlus suggests choosing the way you would for your mother: get referrals (nurses and scrub techs know who is good), meet two to four providers, judge rapport and shared goals, and review before-and-after galleries. Skilled PAs, nurses and family doctors can be excellent injectors. For eyelid surgery, he suggests starting with oculoplastic surgeons.

#10 – Matt Kaeberlein, Ph.D.: rapamycin and dogs — living longer, healthier & turning back the clock

Guest: Matt Kaeberlein
Date: 2019-12-23 · Duration: 1:32:53
URL: https://www.youtube.com/watch?v=kE-ep1kBziQ

KEYPOINTS

• A seminar in his first semester steered Kaeberlein toward aging

Trained in biochemistry and mathematics and planning a career in structural biology, Kaeberlein heard Lenny Guarente talk about the genetics of aging at MIT. His PhD work went on to show that boosting Sir2 extended lifespan in yeast. A year later, Heidi Tissenbaum showed the worm version did the same, the first conserved genetic regulator of lifespan across such distant species.

• Pet dogs are a better step toward humans than lab mice

Lab mice are inbred and live in controlled cages. Companion dogs are genetically diverse, share our homes and get many of the same age-related diseases; cancer is their top killer, and big dogs get more of it. Kaeberlein also argues that people will believe aging can be slowed far more readily when they see it in their own dog than in a news article.

• Treating healthy individuals demands a very low tolerance for side effects

Geroscience aims to intervene before disease, the reverse of traditional medicine, so regulators and the public accept little risk. Kaeberlein argues society should debate that standard, because a 'healthy' 70-year-old isn't the same as a healthy 30-year-old and we know what happens if aging goes untreated.

• Intermittent dosing may boost immunity rather than suppress it

Joan Mannick's study gave healthy older people the rapamycin analog everolimus at 20 mg weekly, 5 mg weekly or 1 mg daily. All three improved their flu vaccine response, with the 5 mg weekly dose doing best with the fewest side effects, and none severe enough for anyone to drop out. Attia notes this runs counter to rapamycin's reputation as a transplant immunosuppressant.

• Short rapamycin courses partly reversed heart aging in old mice

In three independent studies, six to ten weeks of rapamycin restored ultrasound measures of heart function in old mice about halfway to young levels, without needing a break from the drug to see the effect. Kaeberlein lists other short-term 'rejuvenation' signals: intestinal stem cells (from a colleague's lab) and the bone around the teeth (from his own). He cautions that doses don't translate cleanly between species.

• Rapamycin's cancer effects depend on dose

Immune surveillance is a major defence against cancer, and it weakens with age. Kaeberlein guesses that moderate rapamycin delays cancer in mice by restoring immune function, while doses high enough to suppress immunity could promote it. Tumours that have already learned to ignore mTOR signals may not respond.

• A 'party dose' revealed striking sex differences

His lab gave mice 8 mg/kg daily injections, the highest dose ever used in an aging study, for three months from 20 to 23 months of age. Males lived about 60% longer after treatment ended, with better muscle function and less cancer. Females gained no lifespan and all died with aggressive blood cancers. He speculates the dose overshot in females, who may be more sensitive to rapamycin, even though the 2009 study that started the field showed a bigger benefit in females.

• Alzheimer's should be treated as a disease of aging

Kaeberlein believes rapamycin has a decent chance in dementia, ideally starting at mild cognitive impairment, but such trials are long and progression is hard to predict. He thinks drugs fail partly because researchers create the disease in young mice. Attia, who doesn't see Alzheimer's as one disease, is most optimistic about the metabolic form. Kaeberlein adds that rapamycin's boost to autophagy (cellular clean-up) might help the harder forms too.

EXAMPLES

• The first rapamycin trial in pet dogs

Healthy dogs at least six years old within a set weight range (roughly 55 in human terms; weight matters because big dogs age faster) received placebo, 0.05 mg/kg or 0.1 mg/kg rapamycin on Mondays, Wednesdays and Fridays for 10 weeks at a Seattle-area clinic. Of 40 dogs screened, 24 finished: 8 on placebo, 11 on the high dose and 5 on the lower dose. Kaeberlein admits the uneven groups reflect inexperience with his first clinical trial.

• One in five 'healthy' dogs had hidden heart disease

About 20% of dogs that seemed healthy had valve leakage visible on ultrasound but not through a stethoscope, forcing a debate with the cardiologist about where normal aging ends and disease begins.

• Heart function improved with no extra side effects

Owner surveys showed no difference in side effects, and blood chemistry didn't change. Increased drinking was reported equally in both groups once the study was unblinded. Two of three heart measures (ejection fraction, fractional shortening and a filling ratio) reached statistical significance, the third had a p-value of 0.06, and dogs that started with the weakest hearts improved most. Kaeberlein says it needs replication.

• The study he'd run with $10–20 million

About 450–500 middle-aged dogs (six to ten years old, over 40 pounds) treated for five years, tracking lifespan and function, including activity measured by GPS collar. More than 6,000 owners signed up with no advertising. He argues lifespan is a meaningful endpoint in dogs because owners euthanize only when a dog is truly sick.

OTHER RELEVANT

• Weekly or intermittent dosing is the strategy being tested

Both the human everolimus data and the dog protocol use intermittent rather than daily dosing to reduce side effects and

possibly favour immune benefits. None of this has established a safe longevity dose for people.

- **A small positive study needs replicating**

  Kaeberlein calls the dog trial about the most positive outcome he could have hoped for, yet it was small and borderline significant. Wait for larger, longer trials before drawing conclusions.

- **A normal exam can miss early heart changes**

  In this study, a stethoscope exam missed heart changes in one in five apparently healthy dogs that only an echocardiogram revealed. The line between age-related decline and disease is often a matter of which test you run.

#02 – Rhonda Patrick, Ph.D.: paradox of IGF-1, ketogenic diets and genetics, benefits of sauna, NAD+

Guest: Rhonda Patrick
Date: 2019-12-17 · Duration: 1:49:49
URL: https://www.youtube.com/watch?v=oXQ9yvGVJDE

KEYPOINTS

• IGF-1 sits in a paradox between growth and longevity.
Higher IGF-1 tracks with more cancer in human polymorphism data, while very low IGF-1 risks frailty and loss of lean mass. Peter describes a right-skewed U-shaped all-cause mortality curve that nadirs around the 70th percentile of IGF-1; above that, the uptick is mostly cancer, while cardiovascular and neurodegenerative risk largely flatline. Peter jokes that living forever at the absolute bottom of IGF is not the clinical goal the U-curve suggests.

• Cycling high and low IGF may beat living permanently suppressed.
Valter Longo's work and short water fasts (including clinical 48-hour protocols around cancer care) sit in this frame: periods of growth alternating with periods of lower IGF, rather than chronic caloric restriction alone. Rhonda notes rodent fasting results are hard to translate because mice lose ~20% body weight in a 48-hour water fast.

• A meaningful minority of keto patients are lipid hyper-responders.
Peter estimates roughly 10–20% of people he has seen on a standard ketogenic pattern—often "e40% of calories from saturated fat, ~40–45% mono—see LDL particle number explode even as triglycerides fall. One relatively young patient who loved keto came back with LDL-P above 3,500 nmol/L. He stresses he has personally seen dozens of patients on keto over his career, so the hyper-responder fraction is not a one-off anecdote.

• Genetics around PPAR pathways may help explain who thrives on keto.
Rhonda discusses PPAR-related fat-metabolism genetics and free vs comprehensive genetic reports as a way to match phenotype to genotype. Both want larger cohorts of hyper-responders genotyped rather than blog debates about whether sky-high LDL-P 'doesn't matter on keto.'

• Exogenous ketone esters can spike blood ketones dramatically.
Rhonda reported going from about 0.1 mM to 6 mM within an hour on a BHB ester—far above the ~0.5–1 mM she sees from overnight fasting or her usual feeding pattern while nursing (often an 11–12 hour eating window). Dom D'Agostino's ketone work comes up as context for how unnatural that spike is compared with fasting physiology.

• VO2 max falls about 1% per year with age—and is trainable.
That ~10% per decade decline roughly parallels age-related muscle loss. A study she cites found 24 sessions of HIIT (about 45 minutes with warm-up/cool-down and hard intervals) raised VO2 max by roughly 12%, enough to offset years of drift.

• Finnish dry-sauna data is dose-dependent and hot.
Observational work (Jari Laukkanen and colleagues) on men using traditional saunas around 175–179°F for ~20 minutes: 2–3 times per week associated with ~20% lower cardiovascular mortality vs once weekly; 4–7 times per week associated with ~40% lower all-cause mortality in the comparison Rhonda recounts. Dementia risk also looked ~20% lower at 2–3 sessions. She contrasts that with infrared cabins that top out near 140°F and cannot reproduce the same thermal load.

• Infrared saunas at ~140°F are not the same stimulus.
She argues you need the high heat and roughly 20 minutes (11 minutes showed smaller effects) to match the Finnish protocols. Sweat-based detox claims get less weight than the cardiovascular and mortality associations.

• Cold after heat is an additive recovery and mood tool.
Her stack is ~20 minutes of sauna then a cold shower or immersion. She has swam in Colorado River water around 42°F when air was hot enough to make it tolerable, and notes 50°F ocean swims of a few hours for a milder version of the same vasoconstriction/afterglow effect. Peter recounts that 42°F swim only worked because air temperature was near 90°F; the same water on a cloudy day would have been untenable.

• Exercise remains hard to beat for brain health.
Despite coming from a deep molecular-biology background, Rhonda says the minimum-effective-dose question for aerobic work plus HIIT keeps winning against supplement stacks when the outcome is brain and healthspan.

EXAMPLES

• LDL-P >3,500 on keto
Peter's young patient case: triglycerides and insulin sensitivity markers looked better, yet particle number and some inflammatory signals worsened—prompting genotype/phenotype curiosity rather than dismissal. Peter refuses the internet claim that particle number is irrelevant whenever someone is in ketosis.

• BHB ester: 0.1 !’ 6 mM in one hour
Rhonda's n=1 ester trial the day before recording, contrasted with ~0.7–0.9 mM from diet-plus-activity and ~1 mM after ~15 hours of fasting when she can manage that window.

• 24 HIIT sessions !’ +12% VO2 max
Roughly 45-minute sessions with five-minute warm-up and cool-down; she uses the result as a practical lever against the ~1%/year age decline. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.

• Sauna dose ladder
2–3×/week ~20% lower CVD mortality; 4–7×/week ~40% lower all-cause mortality in the Finnish men comparisons she cites, with dementia associations in the same literature.

• Lemur caloric-restriction Nature study
Discussed early: CR raised median and maximum lifespan in the lemur model (on the order of an extra year against a ~11–

12 year maximum), as part of reframing growth vs restriction.

OTHER RELEVANT

- **If lipids explode on keto, measure particles—don't hand-wave.**
  Track LDL-P or apoB, inflammation, and consider genetic context. Loving the diet is not the same as a clean risk profile. The conversation keeps the claim tied to named mechanisms, numbers, and caveats so a listener can act or ask better questions without flattening the nuance.
- **Prefer Finnish-style heat over lukewarm infrared claims.**
  Aim near 175°F+ for ~20 minutes, several nights a week if tolerated, rather than assuming a 140°F IR cabin matches the epidemiology. Eleven minutes helped in the Finnish data, but twenty minutes carried the stronger association she wants people to copy.
- **Pair heat with cold and protect sleep with a temperature drop.**
  Sauna then cold shower, then a cool bed, uses a steep temperature gradient to fall asleep faster—an effect both endorse from experience.
- **Think in IGF cycles, not permanent suppression.**
  Training, protein, and occasional fasting create ups and downs; living forever at the bottom of the IGF curve is not the goal their data sketch.