Clinical Trials to Treat *Aging*?

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Welcome to Issue 40 of Science Says! Our weekly newsletter where you'll learn the latest healthy aging and C15O research news that our team of doctors, scientists, and experts are most excited about—without having to go search for it.

Eric and Steph
Co-Founders, Doctors, Nerds

What Dr. Nik Schork, one of our Lead Scientists and author of over 300 peer-reviewed scientific publications, is reading.

HEALTHY AGING

Testing Therapeutics to Delay Aging

In the *Annals of the New York Academy of Sciences*, DeVito et al. summarize the outcomes of a symposium on **geroscience and geroprotectors (aka anti-aging science and anti-aging therapeutics).** For this series, we're sharing the latest and greatest thoughts on how to discover holy grail geroprotectors that could meaningfully delay aging to improve our healthspan and longevity.

So, how do you validate anti-aging compounds?

That's the question posed by the National Institutes of Health (NIH)'s Geroscience Network, which is a group of over a dozen aging centers throughout the United States and beyond. This prestigious team got together to define how geroprotectors could best be evaluated, with a focus on clinical trials. The result? A paper entitled, "Strategies and Challenges in Clinical Trials Targeting Human Aging," published in the *Journals of Gerontology.*

First up, what are the goals of clinical trials to delay aging?

The group concluded that the desired outcome of an ideal geroprotector is to enable ourselves and our loved ones to maintain independence and quality of life for as long as possible. The best way to do that is to find interventions that have broad effects on:

- **Many different age-related diseases**, including diabetes, heart disease, Alzheimer's disease.
- **Many different age-related syndromes**, such as falls, immobility, and frailty.
- **Age-related declines in physiological functions**, including fundamental aging mechanisms that predispose us to multiple chronic diseases and affect the physiological function of many organ systems.

At this meeting, the group agreed that the goal of geroprotectors is to increase the number of years we are healthy (aka, our healthspan). If that also helps us to increase our longevity, bonus points to the geroprotector.

Okay. But how do you measure if a geroprotector is actually working?

The ultimate clinical trial for a geroprotector would be a randomized, double blinded, placebo controlled clinical trial over a long period of time including large study population to test for the following "hard" outcomes: 1) lowered burden of chronic disease, 2) maintained independence, and 3) well, not dying.

Well, that seems difficult. Are there other options in the meantime?

While large clinical trials are underway (including the TAME trial with metformin), the Geroscience Network came up with some quicker ways to start finding holy grail geroprotectors. This included finding interventions that offer the following in humans:

- ☑ Evidence that it can reverse the aging process (like, stopping age-related cell breakdown)
- ☑ Biological data showing that it targets basic aging mechanisms (like, repairing mitochondria)
- ☑ Cause positive changes in clinically relevant biomarkers (like, reducing inflammation)
- ☑ Provide great tips for larger clinical trials

Here's the geroprotector leaderboard.

Based on the criteria above, here is the small handful of molecules that have made the geroprotector leaderboard:

- Rapamycin
- Acarbose
- Metformin
- Aspirin
- 17-α-estradiol
- Nordihydroguaiaretic acid

What do all of these compounds have in common? They are prescription drugs FDA-approved for various clinical indications, but may be able to do much more.

Completed geroprotector clinical trials

In the *Frontiers in Aging*, Nielsen et al. review completed clinical trials targeting aging. Interventions that have completed tested in clinical trials include the following:

- **Caloric restriction.** Clinical trials showed that simply restricting our caloric intake can effectively lower glucose, blood pressure, resting metabolic rate, insulin, cholesterol and body mass. It also increased mitochondrial function and decreased DNA methylation pace of aging.
- **NAD+ supplements.** When taken alone, nicotinamide riboside supplementation increased NAD levels, increased mitochondrial function, and lowered pro-inflammatory cytokines, including IL-2, IL-5, IL-6, TNFα, IL-1B, and IL-18. In two studies, it had no effect.
- **Senolytic drugs** (dasatinib and quercetin, D+Q). These clinical trials showed that D+Q improved gait speed and walking distance, and lowered pro-inflammatory cytokines, including IL-1α, IL-2, IL-6, IL-9, MMP-2, MMP-9, and MMP-12.
- **Urolithin A.** A clinical trial with urolithin A focusing on aging demonstrated that this mTOR inhibitor present in pomegranate juice increased mitochondrial function.

Bringing it home

In summary, we have a solid understanding of how aging works - and better yet - how to reverse aging to slow the onset of chronic diseases and live healthier, longer. Clinical trials are ongoing and will take time, but there are interim steps that are helping to narrow down leading geroprotectors. Aside from caloric restriction, completed clinical trials specific to aging have been less exciting than hoped. The hunt for the holy grail geroprotector continues.

Yes, we are building up to a(nother) big C15O story.

This week, we snuck in a review on anti-aging clinical trials. Next week, we'll talk about how the world's smartest scientists are approaching the hunt for the perfect geroprotector - from genotype to phenotype. Basically, how do we actually translate promising discoveries in the dish to meaningful healthy aging interventions that will be available in our lifetime?

Take notes on this series. Because at the end there will be a quiz...and an exciting announcement about our latest C15O research.

Have a wonderful week, everyone!

Dive deeper into the science

READ THESE STUDIES

- Symposium report on geroscience & geroprotectors
- Strategies and Challenges in Clinical Trials Targeting Human Aging
- Clinical Trials Targeting Aging
- Biohacking Conference
- Check out all the C15:0 science at www.discoverC15.com