

Anti-aging interventions on Mice, ITP, and LEV Foundation | January 2023 | N°166 | The Death of Death

Healthy longevity research is crucial for ensuring that as we live longer, we are to live better. By understanding the complex processes of aging and disease, we can develop strategies to promote healthy aging, allowing individuals to live longer lives in good health. This not only improves the quality of life for individuals but also helps to reduce the burden on healthcare systems and maintains economic and social stability. Investing in healthy longevity research is an investment in our collective future

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This month's theme: Anti-aging interventions on Mice, ITP, and LEV Foundation

Remark: This month's newsletter is more on the technical side so please feel free to contact [us](#) for further clarification wherever needed.

Aging is a complex and multifactorial process. There are countless theories about why and how aging occurs and many claims to be able to stop the aging process and thus increase lifespan.

Laboratory mice are preferred for research on aging is their short life span, which allows for faster results. Various experiments carried out on mice, as well as numerous genetic interventions, have yielded significant results and have led to a better understanding of the fundamental processes of aging.



Multiple rules and regulations must be followed to ensure that ethics are maintained while using a model organism for experimental purposes. The EU has a set of strict rules and suggestions which must be followed, these are [the three Rs](#)- Replacement, Reduction, and Refinement-

Concerning the efficiency of tests, ideally, researchers should follow four main rules:

- Registration of the interventions before starting. This is useful to give ideas to other researchers and to be complete in the description of the goal of the experiment *in tempore non suspecto* (before other people comment or contest the results).
- Publication of the results, even if unsuccessful. The publication of unsuccessful trials is very useful to "close doors" and give ideas to other researchers as well.
- Use old mice and keep them alive until they die to be able to measure the real-life extension effect
- Make experiments with a control group of mice and ideally in a ["blinded" environment](#).

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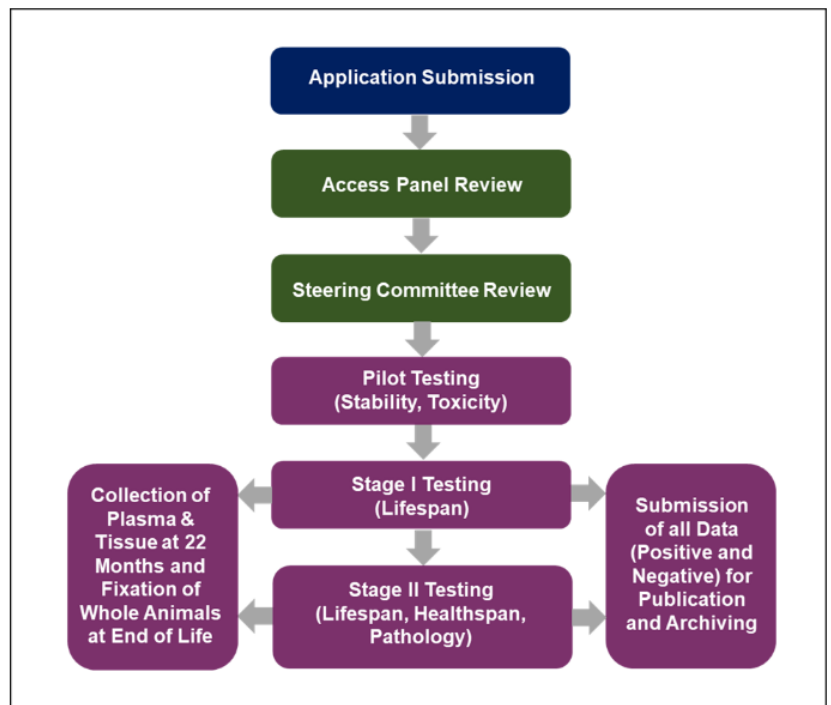
A list of the main ongoing and upcoming interventions are:

- [Rapamycin treatment](#)
- [Metformin](#)
- [NAD+ Supplementation](#)
- [Growth hormone receptor antagonist treatment](#)
- [Methionine restriction](#)
- [Telomerase activation](#)
- [Stem cell therapy](#)
- [Blood Dilution](#)
- [Gene editing using CRISPR-Cas9 technology](#)
- [Sirtuin activation](#)
- [Caloric restriction](#) (and mimetic)
- [Exercise](#)
- [Mitochondrial uncoupling](#)
- [Mitochondrial biogenesis](#)
- (Maybe in a close future) [Rejuvenation by ultrasound](#)

Details of each can be found in the [Scientific Fact Sheet](#): Importance of mice and rats in longevity research.

[The Interventions Testing Program \(ITP\)](#)

The Interventions Testing Program (ITP) started in 2012 under [the Division of Aging Biology](#). The main goal is testing potential agents that may delay aging as measured by lifespan extension and/or delayed onset/severity of late-life pathologies. The three testing sites Jackson Laboratory, the University of Michigan, and the University of Texas Health Science Center at San Antonio work closely together with the National Institute on Aging (NIA) to design and execute standard operating procedures (SOPs) that provide consistent experimental protocol adhered to across the program. It is interesting to note that scientists at ITP have mentioned that the data and results collected from all three laboratories often show “significant” differences even when all the parameters are set exactly the same for reasons they do not understand.



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Each site also brings specialized expertise to the project, including statistical analysis, pharmacology, toxicology, and optimal diet compounding. The UM-HET3 mice are genetically heterogeneous, the equivalent of a large sibship. Each mouse is observed until its natural death or until it becomes so severely ill that survival for more than an additional week seems very unlikely. The study design includes sufficient numbers of mice to provide 80% power to detect a 10% increase in average lifespan in either sex.

They have so far identified [nine agents that significantly increase median lifespan](#) — acarbose ([Harrison 2014](#), [Strong 2016](#), [Harrison 2019](#)), aspirin ([Strong 2008](#)), canagliflozin ([Miller 2020](#)), captopril ([Strong, 2022](#)), glycine ([Miller 2019](#)), nordihydroguaiaretic acid (NDGA) ([Strong 2008](#), [Strong 2016](#)), Protandim® ([Strong 2016](#)), rapamycin ([Harrison 2009](#), [Miller 2011](#), [Wilkinson 2012](#), [Miller 2014](#)) and 17 α -estradiol ([Harrison 2014](#), [Strong 2016](#), [Harrison 2021](#)).

The ITP constantly publishes all the data, including data collected on agents that fail to increase lifespan or delay late-life illnesses, or interventions that have deleterious side effects.

Collaborative Interactions Program

[The collaborative Interactions Program \(CIP\)](#) was established to provide samples from ITP studies to advance aging research through collaborations with other scientists in the United States and in other countries. These samples are available free of charge (except, in some cases, for shipping charges). Plasma and certain frozen tissues are available from mice sacrificed at 22 months of age in all treatment and control groups from [Cohorts 2015 to the present](#).

[Longevity Escape Velocity Foundation \(LEV Foundation\): Robust Mouse Rejuvenation Study](#)

LEV Foundation is performing large mouse lifespan studies, with the administration of four interventions namely Rapamycin, Senolytic, mTERT, and HSCT. All of these have individually, shown promise in extending mean and maximum mouse lifespan and health span. Their main focus is to test interventions that have shown efficacy when begun only after the mice have reached half their typical life expectancy, and mostly on those that specifically repair some category of accumulating, eventually pathogenic, molecular, or cellular damage.

The first study in this program is starting in January 2023.

Goals and Motivations

LEV Foundation's ultimate goal in this program is to achieve "Robust Mouse Rejuvenation". The interventions will be applied to mice of a strain with a mean lifespan of at least 30 months and initiated at an age of at least 18 months. The goal is to increase both mean and maximum lifespan by at least 12 months. In each study in this program, the Foundation will examine the synergy of (typically at least four) interventions already known individually to (probably) extend mouse lifespan when started in mid-life. They will determine not only the ultimate readout of lifespan but also the interactions between the

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various interventions, as revealed by the differences between the treatment groups (receiving different subsets of the interventions) in respect of the trajectories with the age of cause of death, the decline in different functions, etc.

Interventions

1. Rapamycin
2. Hematopoietic Stem Cell
3. Transplant Telomerase Expression
4. Senescent Cell Ablation

Experiment Schedule:

The LEVF will sacrifice 12 mice out of each group of 50 (males or females, for each of the ten treatments) for analyses that require terminally invasive tissue samples. In contrast to most studies, it will schedule these based not on chronological age but on group-specific survival curves. The LEVF believes this will be more informative than the traditional approach since the underlying correlation between biological and chronological age is factored out.

The LEVF considers there is a major chance that the most efficient interventions will be multi-component. That is why there will be 10 groups of mice tested:

1. Controls only
2. Rapamycin only
3. Senolytic only
4. mTERT only
5. HSCT only
6. All but Rapamycin
7. All but Senolytic
8. All but mTERT
9. All but HSCT
10. All interventions

Other interventions in the future will concern

1. Sapheresis or Plasma Dilution
2. Next-Generation Senolytic
3. T-cell rejuvenation
4. Environmental enrichment

A bright future for mice and humans?

Thanks to the tests organized by the LEVF and hopefully soon other organizations, we could know soon what is useful for the healthy longevity of old mice. And a bit later, for

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Good News of the month: Half-life more for old mice gene therapy.

Bad News of the Month: Longevity treatments do not slow aging. Mortality increasing in Europe and China. Currently, the oldest person in the world is only 115 years old.

[Recent studies](#) have demonstrated that partial reprogramming using the Yamanaka factors (or a subset; *OCT4*, *SOX2*, and *KLF4*; *OSK*) can reverse age-related changes *in vitro* and *in vivo*. They show that systemically delivered AAVs, encoding an inducible OSK system, in 124-week-old mice extend the median remaining lifespan by 109% over wild-type controls and enhance several health parameters.

[In a new study](#), researchers have taken a close look at three treatment approaches that have been widely believed to slow the aging process. However, when tested in mice, these treatments proved largely ineffective in their supposed impact on aging. "There is no internal clock of aging that you can regulate with a simple switch -- at least not in the form of the treatments studied here," concludes Dr. Dan Ehninger of the DZNE, the initiator of the study.

The mortality in China in 2022 was the [highest since 1976](#). The mortality in the European Union was [higher in 2022](#) than before the Covid.

The French [sister André](#) died on January 17 at the age of 118 years. [Maria Branyas Morera](#), who now became the dean of humanity, is "only" 115 years old, the lowest age in the world since 2012.

For more information

- [Heales](#), [SENS](#), [Longevity Alliance](#), [Longecity](#), and [Lifespan.io](#)
- [Heales Monthly Science News](#)
- [Source of the image](#)