Aging Pathobiology and Therapeutics 2022; 4(2): 51-52 ***51***
DOI: 10.31491/APT.2022.06.086

COMMENTARY

Pharmaceutical interventions to slow human aging. Are we ready for cocktails?

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Abstract

Slowing human aging with pharmaceuticals is now recognized as a feasible strategy. However, the design of clinical trials is still focused on single drug approaches. The process of aging has multiple pathways, which no current drug has been shown to effectively target. Therefore, it is of interest to study combinations, or cocktails, of drugs. A recently published article reported that a drug cocktail of rapamycin, acarbose and phenylbutyrate slowed aging in middle-aged mice treated for three months. The impact of this report is discussed, with the implications for determining endpoints in humans for testing drug cocktails as well as testing other drug combinations.

Keywords: Healthy aging, drug cocktail, aging mice, rapamycin, acarbose, phenylbutyrate

A panel of experts held a workshop in 2013 in Erice, Italy entitled "Interventions to slow aging in humans: are we ready yet?" The panel selected a subset of the most promising strategies that could be tested in humans for effects on enhancing healthy aging [1]. Among these were specific pathways associated with aging that were targeted by one or more repurposed drugs, ie., drugs that had already been approved for clinical use for other disease entities. The pathways included mTOR, AMPK, histone deacetylase (epigenetics), and generic inflammation, as well as others. Several drugs were mentioned, such as rapamycin and metformin, that were considered safe for clinical trials in older people. What was not discussed at the time was the challenge of targeting multiple processes of aging with just one drug.

To address this issue, we published an editorial entitled "Testing drug combinations to slow aging" [2] promoting the concept that in order to effectively slow aging, combinations of drugs were going to be needed. The rationale behind using a combination of drugs is that multiple pathways are involved in aging, which will require drug cocktails to target these pathways in order to effectively slow aging (Figure 1). Currently, there is no single drug that can target the multiple pathways involved, and whether at some point in the future there will be is not known. Drugs, such as rapamycin and acarbose, that have previously been shown to extend lifespan in mice [3] are of interest because they target different aging pathways.

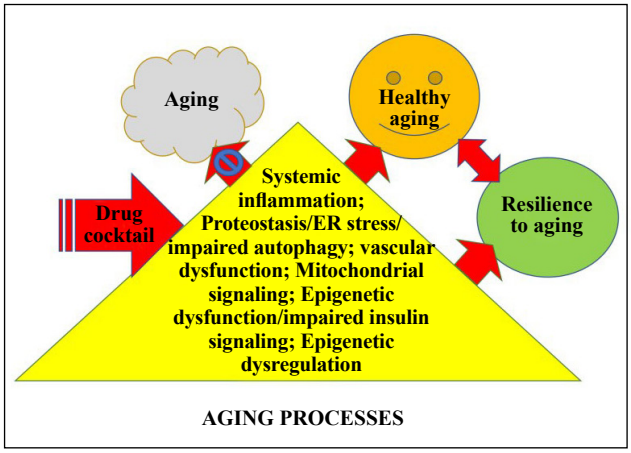

Figure 1. A drug cocktail that targets multiple aging processes will enhance resilience to aging.

Testing drugs in mouse lifespan studies has been the gold standard but is costly and time consuming as well as having complicated translational relevance. A new approach has been developed where middle-aged mice can be treated with a promising drug for several months and the anti-aging effects of the drug can be assessed by changes in the

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Received: 21 June 2022 / Accepted: 24 June 2022
Published: 30 June 2022

severity of age-related lesions [4]. This approach can be used for testing drug cocktails.

Jiang *et al*. [5] published a study in middle-aged mice treated for three months with a combination of rapamycin, acarbose, and phenylbutyrate and showed the cocktail to be superior to any of the individual drugs in slowing aging as defined by decreased age-related lesion severity as well as increased physiological performance. The drug cocktail targets multiple pathways of aging. Rapamycin targets autophagy and vascular deficits, acarbose indirectly targets insulin signaling and oxidative stress, and phenylbutyrate targets protein folding and histone deacetylase (epigenetic) activity. The study used C57BL/6 middle aged mice as they are a popular preclinical model for aging research, and HET3 four-way cross mice as they were utilized by the NIA Intervention Testing Program to show the drugs used in the study extended lifespan. The study showed that similar effects of slowing aging were observed in this strain as in C57BL/6 mice, thus providing validation for the short-term effects of the drug cocktail.

These results are very promising and demonstrate the effectiveness of a drug cocktail over a single drug in slowing aging. The cocktail serves as an excellent prototype, but is it the ultimate pharmaceutical combination to enhance healthy aging? Most likely not, as each of the three drugs did not contribute equally to the overall effects of the cocktail, with rapamycin seemingly contributing the most. Therefore, several of the drugs could be replaced by other drugs, or additional drugs could be added, and tested in the same mouse model system.

An equally important feature of the study was the reduction in study time by starting with middle-aged mice on a three-month treatment regimen. This, of course, requires having access to middle-aged mice, which is possible in the United States through the National Institute on Aging Aged Rodent Colony. Are the positive results of the short-term study in middle-aged mice translationally relevant? The implications are yes. A 3-month study in mice would be roughly equivalent to a 6-year study in middle-aged people. Moving from mouse studies to clinical trials brings up many questions, such as who gets the drug cocktail and at what point should people start taking the drug cocktail.

But more importantly, what would be the endpoints for determining the effectiveness of the cocktail in middle-aged people who necessarily will not have strong age-related dysfunctions? Certainly, assessing the severity of age-related lesions would not be as comprehensive since autopsies for accessing multiple tissues would not be a part of any short-term study. Biopsies, such as skin and possibly a few other tissues, and peripheral white blood cells would be accessible. The use of serum protein biomarkers for aging would be of high interest in these types of studies, but unfortunately have not been fully developed and validated yet, therefore more research is needed in this area.

So, are we ready for clinical trials to see if drug cocktails can enhance resilience to aging in middle-aged people? The study by Jiang *et al*. [5] provides promising evidence that cocktails work in middle-aged mice and paves the way for more comprehensive studies in mice and preliminary studies in humans.

Declarations

Author contributions: The authors contributed equally to writing this manuscript.

Availability of data and materials: Not applicable.

Financial support and sponsorship: Grants NIH R56 AG058543, Ladiges (PI); NIH R01 AG057381, Ladiges (PI).

Conflicts of interest: Warren Ladiges is a member of the Editorial Board of *Aging Pathobiology and Therapeutics*. The author declares that there are no conflicts.

Ethical approval and informed consent: Not applicable.

Consent for publication: Not applicable.

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Cite this article as: Rosenfeld M, Ladiges W. Pharmaceutical interventions to slow human aging. Are we ready for cocktails? *Aging Pathobiol Ther*, 2022, 4(2): 51-52. doi: 10.31491/APT.2022.06.086