SHARING INSIGHTS, SHAPING INVESTMENTS, BUILDING OUR GEROFUTURES

For decades, the American Federation for Aging Research (AFAR) has been dedicated to its mission of advancing and supporting healthy aging through biomedical research. By sustaining the pipeline of rigorous research, AFAR has helped build the foundation of knowledge in the biological processes of aging and how they drive age-related diseases.

Thanks to the insights of scientists and collaborations supported by AFAR, this geroscience is poised to move from the labs into our lives through promising therapeutic interventions. Through this, we envision “gerofutures” filled with vitality and longevity.

AFAR has supported science and convened researchers worldwide and is committed to advancing collaborations that help break down barriers that impede scientists, institutions, and organizations from applying what science shows us.

In 2021, AFAR’s International Activities Task Force invited leaders from around the world and across the scientific, philanthropic, policy, and biotechnology sectors for a series of invigorating conversations.

The GeroFutures Think Tanks brought together scientists, funders, and entrepreneurs from Australia, Israel, the Netherlands, Singapore, the United Kingdom, the United States, and beyond to share their insights and wrestle with tough questions about the main challenges and most promising areas facing aging research. (Since the sessions were conducted in accordance with Chatham House Rules, the sources or speakers are not explicitly or implicitly identified in each summary here.)

The three Think Tanks explored:

• SUPPORTING BASIC SCIENCE AND GEROSCIENCE
• INVITING INVESTMENT IN GEROTHERAPEUTICS
• PREPARING THE TRANSLATIONAL RESEARCH PIPELINE

This report summarizes key insights from each while asking what’s needed next. Across the three Think Tanks, two major takeaways emerged consistently:

• The need for an F.D.A. indication for aging and improved regulatory pathways, which would open the door to promising therapeutics and potential investments, and
• The need for international collaboration between private and research sectors, as well as interdisciplinary research on aging.

Additionally, this report explores the socioeconomic impact of extending healthspan and reminds that promising therapeutics rely on the pipeline of biomedical research in the processes of aging.

AFAR hopes that this GeroFutures Think Tanks report encourages knowledge sharing, fosters potential collaborations and investments, and inspires innovative new approaches to aging research.

Please consider joining us in supporting this critical work to turn today’s breakthrough discoveries into tomorrow’s transformative interventions.

Stephanie Lederman, EdM
AFAR Executive Director

Richard G.A. Faragher, BSc, ARCS, DPhil
AFAR board member; Professor of Biogerontology
School of Pharmacy & Biomolecular Sciences,
University of Brighton
THINK TANK I
SUPPORTING BASIC SCIENCE AND GEROSCIENCE

Chair
Richard G. A. Faragher, BSc, ARCS, DPhil: Professor of Biogerontology at the University of Brighton; AFAR board member.

Participants
Gil Atzmon, PhD: Associate Professor in the Departments of Medicine and Genetics at Albert Einstein College of Medicine.

Nir Barzilai, MD: Director of the Institute for Aging Research and Director of Nathan Shock Center for the Excellence in the Basic Biology of Aging at Albert Einstein College of Medicine; AFAR Scientific Director and multiple grantee.

Haim Cohen, PhD: Head of Molecular Mechanism of Aging Lab, Director of the National Metabolic Center for Excellence in Scientific Research in Human Diseases, Director of the Israeli-German Minerva Center for Study of Biological Mechanisms of Aging, and Director of the Sagol Healthy Longevity Center at Bar Ilan University.

David Le Couteur, MD, PhD: Director of the Centre for Education and Research on Ageing (CERA) and Director of the Biogerontology Laboratory of the ANZAC Research Institute at the University of Sydney.

Lynne Cox, PhD: Associate Professor in the Department of Biochemistry at the University of Oxford; Royal Society of Biology Fellow; Co-founder of the Oxford Ageing Network.

Ana Maria Cuervo, MD, PhD: Co-Director for the Institute for Aging Research, and Robert and Renée Belfer Chair for the Study of Neurodegenerative diseases at Albert Einstein College of Medicine; AFAR board member and grantee.

Stathis Gonos, PhD: Director of Research at the National Hellenic Research Foundation/ICB, E.U; Editor-in-Chief of “Mechanisms of Ageing & Development.”

Brian Kennedy, PhD: Director of the Centre for Healthy Aging at the National University Health System, Singapore; Professor, Buck Institute for Research on Aging; AFAR grantee.

Janet Lord, FMedSci: Director of the Institute of Inflammation and Ageing and Director of the MRC- Versus Arthritis Centre for Musculoskeletal Ageing Research at the University of Birmingham.

Andrea B. Maier, MD, PhD, FRACP: Oon Chiew Seng Professor in Medicine, Healthy Ageing and Dementia Research, and Co-Director of the Centre for Healthy Longevity at the National University of Singapore, Singapore; Professor of Gerontology at Vrije Universiteit Amsterdam, The Netherlands.

S. Jay Olshansky, PhD: Professor in the School of Public Health at the University of Illinois at Chicago; Research Associate at the Center on Aging at the University of Chicago and at the London School of Hygiene and Tropical Medicine; Chief Scientist at Lapetus Solutions, Inc.; AFAR board member.

THINK TANK II
INVITING INVESTMENT IN GEROTHERAPEUTICS

Chair
Jim Mellon: Chairman and Co-Founder of Juvenescence; AFAR board member.

Participants
Kristen Fortney, PhD: Co-Founder and CEO of BioAge; AFAR grantee.

Jamie Gibson: CEO and Director of Regent Pacific.

Mehmood Khan, MD: CEO of the Hevolution Foundation; CEO of Life Biosciences; recent AFAR board member.

Sergey Young: Founder, The Longevity Fund; AFAR board member.

THINK TANK III
PREPARING THE TRANSLATIONAL RESEARCH PIPELINE

Chair
Richard G. A. Faragher, BSc, ARCS, DPhil: Professor of Biogerontology at the University of Brighton; AFAR board member.

Participants
Shai Eyfratti, MD: Director of Research and Development, and Head of Nephrology at the Sagol Center for Hyperbaric Medicine and Research at Sharmir Medical Center.

Lorna Harries, PhD: Co-Founder and Chief Scientific Officer, SENISCA.

James L. Kirkland, MD, PhD: Director of Robert and Arlene Kogod Center on Aging, and Noaber Foundation Professor of Aging Research at Mayo Clinic; AFAR President and grantee.

Sean Leng, MD, PhD: Professor in the Division of Geriatric Medicine and Gerontology in the Department of Medicine at Johns Hopkins University School of Medicine; President of the Milstein Medical Asian American Partnership Foundation (MMAAP); AFAR grantee.

Andrea B. Maier, MD, PhD, FRACP: Oon Chiew Seng Professor in Medicine, Healthy Ageing and Dementia Research, and Co-Director of the Centre for Healthy Longevity at the National University of Singapore, Singapore; Professor of Gerontology at Vrije Universiteit Amsterdam, The Netherlands.

Joan Mannick, MD: Head of Research and Development, Life Biosciences.
WHAT IS THE MOST IMPORTANT CURRENT AREA OF RESEARCH IN THE BASIC BIOLOGY OF AGING?

Several experts concurred that research targeting the mechanisms or hallmarks of aging remains at or near the top of the list. Of particular interest is improving our understanding of which hallmarks, or combinations of them, drive distinct, aging-related diseases and multi-morbidity clusters in older people.

Epigenetics, the study of how your behaviors and environment can cause changes that affect the way your genes work, came up repeatedly during the session. The need to harness big data and artificial intelligence (AI) to better understand the biology of aging and help create preventive medicines and develop personalized treatments came up as well.

Another focus for current research involves gaining a better understanding of why loss of homeostasis occurs in aging. We need to define what are normal changes in aging humans before we can diverge into unhealthy aging and the diseases of aging.

And while research using animal models remains important, the work going on in human models is most likely to move in the direction of therapeutic interventions.

WHAT AREA OF RESEARCH IN THE BASIC BIOLOGY OF AGING IS MOST LIKELY TO EMERGE AS THE “NEXT BIG THING”?

Centenarians appear to be a particularly promising subgroup of the population to study. Learning how and why they not only live much longer, but live much healthier longer—with a contraction of morbidity, even though they often carry genes known to cause disease—could tell us much about decelerating aging.

Immunosenescence, the cellular changes in the immune system associated with aging, is another area ripe for further study to identify ways that improving the immune system could either slow or reverse aging.

Other targets include examining the microbiome and how it interacts in determining whole body health and aging; studying why women get back to homeostasis after pregnancy, and building on those findings to understand loss of homeostasis in aging; tapping the power of big data to understand the processes of aging in order to develop personalized treatments; and exploring cellular reprogramming to restore function.

“Some of the most exciting work is focused on humans. That’s not to say that the work that’s going on on other species isn’t critically important. It is, absolutely. But if you’re asking me what’s likely to move in the direction of a therapeutic intervention, I think that the work going on in humans is some of the most critical work that’s going on now.”
WHAT PARTICULAR STRENGTHS DOES YOUR COUNTRY HAVE IN RESEARCH IN BASIC BIOLOGY OF AGING? ASSUMING EXTRA FUNDING WAS AVAILABLE, WHAT ADVANTAGES CAN YOU SEE FROM INTERNATIONAL COLLABORATION?

Experts highlighted networks and centers in several countries, including the Nathan Shock Centers of Excellence in the Basic Biology of Aging in the U.S., which allows aging experts in different parts of the country to work together. Another example was the Charles Perkins Centre in Australia, which now has a strong focus on aging and nutrition.

Biobanks with extensive phenotypic data from large cohorts were cited by experts from the United Kingdom and the Netherlands. For example, the University Medical Center Groningen’s LifeLines study has a biobank with phenotypic data from a multigenerational cohort that includes over 167,000 participants from the northern population of the Netherlands.

In addition to biobanks, other strengths in the U.K. included patient health informatics, with hospital data now beginning to be linked with primary care data, and genome sequencing capacity. Israel was noted to have strengths in genetic diversity, central medical database, phenotype medical system, economic progress, a growing aging population, and top life expectancy.

All spoke strongly in favor of overcoming obstacles to increased international collaboration.

WHAT IS ONE REAL AND/OR PERCEIVED BARRIER TO FURTHERING THE BIOLOGY OF AGING AND GEROSCIENCE IN YOUR COUNTRY, AND HOW CAN WE POTENTIALLY ADDRESS THESE BARRIERS?

The fundamental barrier most often cited across countries and continents was inadequate funding. That is especially true for aging research in particular and for international collaborations among academic institutions.

Experts from several countries noted that aging research does not have a high profile among their government funding agencies. The point also was made that arming researchers with detailed projections for various countries showing the economic benefits of increasing healthspan would help them make the case for funding.

Other barriers identified included grant reviewers—including government officials, and clinicians, among others—who lack understanding of the concept of targeting aging to improve health.

Other key obstacles discussed: convincing the U.S. Food and Drug Administration (F.D.A.) to accept aging as an indication for therapeutics, and adding aging biology to medical curricula at the preclinical level so emerging clinicians understand, early in their careers, that aging can be targeted.

WHAT’S NEEDED NEXT

• Foster international collaboration among aging researchers
• Promote the idea of funding networks of laboratories (possibly across continents) to reach a critical mass of researchers from different disciplines working together, while accessing biobanks with phenotypic data from a different set of people
• Ramp up studies in centenarian subgroup of populations
• Improve understanding, among key funding and clinical influencers, that aging can be targeted
Inviting Investment in Gerotherapeutics

WHAT BIOLOGICAL DISCOVERIES ARE MOST LIKELY TO INTEREST INVESTORS IN LONGEVITY? WHY DO YOU THINK THIS?

Investors generally are interested in discoveries that hold promise in the near term: those involving such breakthroughs as biological aging clocks and biomarkers are especially hot now. Understanding the pace of aging will permit standardized measurement of individual aging rates as well as the effectiveness of personalized interventions designed to help us age successfully. This holds true whether the intervention is based on lifestyle (diet or exercise), social (socio-economic circumstances), or pharmaceutical approaches. Access to such data not only increases opportunities for therapeutics but also unlocks future investment opportunities.

Also attractive to investors is research confirmed by multiple labs independently; for example, studies of compounds in mice that could be parabiotic factors or that destroy senescent cells.

Investors also want to see a practical clinical path forward. Meaning: the intervention may target a particular disease with an approved indication for therapeutics, but research also suggests it can affect the aging process and the biology of aging underneath it. That, in turn, offers the promise that it’s going to affect other pathways and other disease processes as well in the future.

Other areas include applying artificial intelligence algorithms to large datasets to develop interventions that slow or reverse aging processes, and epigenetic reprogramming, viewed as a promising field, but not as close to translation.

WHAT, IF ANY, REGULATORY CHANGES ARE NEEDED TO ENHANCE THE PROSPECTS OF SUCCESS FOR PRODUCTS OR SERVICES THAT ARE DEVELOPING FROM OUR ENHANCED UNDERSTANDING OF THE BIOLOGY OF AGING? WHY DO YOU THINK THIS?

Convincing the U.S. Food and Drug Administration (F.D.A.) to recognize aging as an indication for therapeutics would create a viable economic model to attract more investment in aging research and development. Moving forward with the TAME (Targeting Aging with Metformin) Trial—a large clinical trial to provide proof-of-concept that aging can be treated, just as we treat diseases—is a critical first step. This would open regulatory doors and provide knowledge about potential biomarkers that will be even more effective at targeting the biological processes of aging underlying most chronic diseases of aging.

Reducing the number of years or decades that it takes to bring a drug to market in the aging field would also spur investment. (Some of the regulatory caution goes back to approvals for early osteoporosis drugs, which improved bone density but later were found to increase the bone fracture rate.) Working with regulators to incorporate surrogate endpoints based on changes to key aging biomarkers would enable clinical trials that establish a human proof-of-concept signal faster and at far less cost.

“We’re looking at 200 companies a year to invest in 10 to 12 possible therapeutics. So our job is actually more about saying no, rather than saying yes.”
WHAT SHOULD EARLY STAGE INVESTORS BE LOOKING FOR IN A COMPANY TO MAKE IT A GOOD PROSPECT, AND WHY?

First is **breakthrough potential**, the likelihood that the discovery or technology will be disruptive and position the company to set the standard of care in the aging field. Because biotech is very risky from an investment standpoint, and any single biotech program is incredibly risky, it’s important that a company has multiple projects in their development pipeline to mitigate that risk.

Next, investors also should consider whether a project addresses an unmet medical need that is large enough to provide a return on the investment. Investors ideally seek a return of at least 10-times their investment to consider it fruitful.

And because many projects in the field may take years to come to fruition, top management needs to have a clear understanding of the inflection points or milestones that must be met in the coming months and years. That includes a direct, clear path to market and addressing regulatory issues and other steps along the way. For investors, that means there must be clearly marked exit ramps.

WHAT IS THE HARDEST THING YOU OR YOUR COLLEAGUES HAVE FOUND ABOUT RUNNING A NEW COMPANY IN THE LONGEVITY OR AGING SPACE?

Resources in the longevity/aging space are tight, and regulatory challenges make the path to success even more difficult. Lacking an F.D.A. indication for aging as a target for new drugs, Big Pharma is hesitant to put its massive Research and Development (R&D) resources into the aging field, focusing instead on disease-specific drugs. That landscape often leads to those in the field making their appeals for investments based on the greater good rather than emphasizing potential returns.

Managing the expectations of a startup company team is hard. Being resource-constrained means companies in the field need to have not just clear “go/no go” milestones in research and development, but also a willingness to move on from projects that aren’t meeting them.

Opportunity costs are crucial. Money spent on a favorite project that is not delivering results may be money not spent on a project that could be transformative.

WHAT’S NEEDED NEXT

- Advance the TAME Trial, which would open regulatory doors to drugs that target the multiple diseases of aging
- Continue building relationships with regulatory agencies such as the F.D.A. to allow more efficient, timely clinical trials for drugs that address key biomarkers of aging
- Convene investors interested in longevity, regularly
There was general consensus across different disciplines on:

- **developing interventions** to delay, prevent, or alleviate age-related diseases as a group, rather than individually, by targeting the mechanisms, or hallmarks, of aging underlying these fundamental diseases;
- **looking at combinations of agents**, rather than just individual agents, that target aging processes and moving them into small, early phase clinical trials that look at multiple conditions in parallel, rather than in series;
- gaining a clearer understanding of exactly how those combinations or individual agents affect the basic mechanisms to extend lifespan; and
- **studying the interaction** between the aging processes and multiple diseases, which leads to vulnerability in older adults.

Two specific areas worth targeting were suggested: **angiogenesis** (the formation of new blood vessels) to address the narrowing and loss of blood vessels that can lead to decline; and **neurogenesis** (the formation of new neurons from neural stem cells) in recognition of the importance of the brain to good health.

The key is to understand the fundamental processes of aging at the very basic level, and then follow where that takes you as far as translation goes.

For the next three to five years, the field needs to demonstrate that what scientists have seen in animal models in the lab can translate into human beings.

One way is by moving promising interventions into early phase clinical trials; for example, combining lifestyle trials (more physical exercise with certain diets) together with repurposed drugs such as Metformin.

And adding placebo-controlled trials to advance the science behind different lifestyle interventions would help establish which ones actually have benefit and which ones don’t.

Expanding aging research to also focus on middle age and look for earlier predictive biomarkers of resilience—whether molecular, cellular, or systemic—could help predict who is more likely to get cognitive dysfunction or frailty, for example, as they get older. This would have a broad public health significance.

“There’s so few clinical trials that are being done, and we have to assume a lot of them are going to fail. That’s part of research and nothing to be afraid of…but you’ve got to bite the bullet and move into human trials to figure it out.”
The U.S. has more funding for aging research than most countries, although it is still insufficient. It also is strong on advanced science and biotech companies with venture funding who understand medicinal chemistry and what it takes to move discoveries into clinical trials and commercial prospects.

The U.K. has free primary health care, and a rich resource of patient data over the lifecourse, while China has a critical mass of aging people for large-scale studies.

Israel's strength is its ability to relatively fast-track translation from different animal models into human beings, while Singapore has not only many ethnicities to study aging processes across populations, but also large amounts of data on environmental factors. However, both Israel and Singapore lack a critical mass of population to conduct large-scale studies, and would need international collaborations to do so.

All participants extolled the benefits of international collaboration for all researchers.

Among the key barriers identified were: lack of adequate funding for aging research; the dearth of pharmaceutical industry support for repurposed compounds, natural products, or lifestyle interventions that are effective, but not patentable; the difficulty of finding information about great research being done in countries all over the world; the lack of identified biomarkers that correlate with functional and clinical improvements in older humans; and not understanding what the public actually wants from aging research and why there is resistance to effective lifestyle interventions.

Suggested ways to overcome these barriers include:
- create an international nonprofit organization to play a role similar to what pharmaceutical companies do in moving interventions through the approval process;
- invest in education and making the field of aging research more attractive to young scientists;
- establish a model, either a successful clinical trial or some type of successful research, that emphasizes the processes of aging; and
- implement more clinical trials: this is the only way to figure out what translates to humans.

WHAT’S NEEDED NEXT

- Create an international infrastructure or nonprofit organization that would be a central clearinghouse for aging research information worldwide and provide regulatory support by playing a role similar to what pharmaceutical companies do in moving interventions through the approval process
- Work to overcome barriers to international collaboration
- Launch a coordinated effort to move more interventions that have shown promise in animal trials into early phase clinical trials in humans
INVESTING IN GEROFUTURES

At large, the GeroFutures Think Tanks remind us of three key areas that are critical to advancing the medical, educational, social, and commercial opportunities that geroscience affords:

**Strengthening the Aging Research Pipeline**

**Securing an Indication for Age-Targeting Therapeutics**

**Applying the Savings of Living Healthier, Longer**

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**THE RESEARCH PIPELINE: SUPPORTING THE SCIENTIFIC FOUNDATION**

The promise of therapeutic interventions is rooted in a foundation in the basic biology of aging.

Thanks to the rigorous scientific research supported by AFAR, we now understand how the processes of aging drive chronic illnesses. And we are poised to move what we’ve learned in the lab into our lives, through interventions that target those “hallmarks” of aging with the promise of delaying or preventing the onset of the most common age-related diseases or conditions.

Strengthening and evolving the pipeline of research in the basic biology of aging, while supporting geroscience that targets the biology of aging and age-related disease, is crucial.

The pipeline of biomedical research in the processes of aging profoundly influences not only the advancement of therapeutic interventions to extend years of health, but also the socioeconomic impact of living healthier, longer.

Learn more about AFAR’s core programs to support the research pipeline at www.afar.org/initiatives

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**THE TAME TRIAL: SECURING AN INDICATION, OPENING DOORS TO THERAPEUTICS**

AFAR is leading the effort to raise funds and launch the TAME (Targeting Aging with Metformin) Trial. Led by AFAR Scientific Director Nir Barzilai, MD, the project aims to provide proof-of-concept that the biology of aging can be targeted through therapeutic interventions.

The multi-site TAME Trial will test whether older adults taking the common diabetes drug Metformin experience delayed development or progression of age-related chronic diseases, such as heart disease, cancer, and dementia. The Geroscience Network of the U.S. National Institutes of Health (NIH) recommended making Metformin the focus of the TAME Trial because of its safety and low cost.

If successful, the TAME Trial would open the door for the F.D.A. to approve “aging” as an *indication*, which simply means a drug is approved for treating a particular condition.

As mentioned by cross-sector participants across the GeroFutures Think Tanks, an indication for aging would unleash the powerful research and development engine of the pharmaceutical and biotech industries, and associated tranches of private and public investments.

This would dramatically shorten the time it takes other transformative interventions to gain approval and reach the people who need them.

To learn more and sponsor the TAME Trial, please visit afar.org/tame-trial
How much money would be saved if geroscience interventions compressed the amount of time spent living with chronic disease—or multiple chronic diseases?

A landmark study published in the July 2021 issue of *Nature Aging*, a leading peer-reviewed journal, employed the Value of Statistical Life methodology used by government agencies to answer that question. The research is co-authored by Andrew J. Scott, DPhil, London Business School; Martin Ellison, PhD, University of Oxford; and AFAR board member and grantee David A. Sinclair, PhD, AO, Harvard Medical School.

The study proposes that a one-year increase in healthy life expectancy is worth an astonishing $38 trillion to the United States, including gains to future generations. At an annual rate, according to their study, that's equivalent to 3.5% of GDP every year.

“The authors suggest that the benefits of aging interventions are much larger than previously thought because increases in healthspan with aging interventions are not linear: they operate in a virtuous cycle,” AFAR board member S. Jay Olshansky, PhD, wrote in a related summary in *Nature Aging*.

“This means that the more successful society is in improving how well we age, the greater the economic value from further improvements.”

This research complements an AFAR-supported study paper in *Healthy Affairs* in 2013, co-authored by Olshansky, and the ongoing promotion of the longevity dividend—the socioeconomic and public health benefits of aging research.

For more on the socioeconomic impact of extending healthspan, visit www.afar.org/what-is-the-longevity-dividend
Find the recent *Nature Aging* articles at www.nature.com/nataging

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**JOIN US**

The American Federation for Aging Research is dedicated and invigorated to fulfill the geroscience promise: we can live not just longer, but live healthier longer.

The remarkable achievements that AFAR has helped guide in aging research over the past 40 years were advanced by the generosity of donors who have invested in the critical work to build the research pipeline that is the foundation of future therapeutic innovations.

To move this research from the labs into our lives requires dedicated collaboration between private, public, and philanthropic investors.

We hope you will consider joining AFAR and our global partners in supporting expert-led science that will transform our GeroFutures.

To support a healthier tomorrow, today, please visit afar.org/donate.
AFAR’s mission is to advance and support healthy aging through biomedical research