Workshop
“Interventions to Slow Aging in Humans: Are We Ready?”
Erice, Sicily, Italy,
October 8–13, 2013.

Chairs:
Luigi Fontana, Donald Ingram, Valter Longo

Local Organizer:
Giampaolo Velo

SPECIFIC AIMS
The main aim of this consensus workshop is to bring together leading experts in gerontology and genetics of aging to begin to obtain consensus related to the discovery and development of safe interventions to slow aging and increase healthspan in humans.

A. CONFERENCE GOALS, BACKGROUND AND JUSTIFICATION

Conference Goals:
-To learn about the major genes and mutations that affect the healthy lifespan.
-To determine the most suitable candidate healthspan interventions/drugs for clinical development and assess their safety after chronic use
-To determine the best leads/avenues for discovery and development of healthspan drugs
-To determine the best markers or risk factors that should be considered to guide drug development
-To establish guidelines on how to develop “pro-healthspan” drugs (e.g. EMA/FDA producing Clinical Development Guidelines for new Drugs).
-To promote interactions between biogerontologists and pharmaceutical companies
-To provide a forum for the discussion of state of the art techniques for drug discovery related to aging and age-related disease
-To stimulate clinical trials to begin the testing of drugs generated by basic biogerontology research and discuss the potential pitfalls and side effects of each drug.

Background
Human aging and age-associated diseases are becoming one of the biggest challenges faced by developed and developing countries. Life expectancy at birth has markedly increased in most developed countries in the last century, from about 45 years at the beginning of the 20th Century to about 77 years today. However, the overall increase in average life expectancy is far greater than that for healthy life expectancy, as evidenced by the incremental burden of age-associated diseases, including
cardiovascular disease, diabetes, hypertension and cancer. The financial burden caused by these chronic diseases is already overwhelming the healthcare and welfare systems of developed nations, and if present trends continue, the challenges could cause even larger problems. In rodents, both dietary restriction (DR) and mutations in nutrient and growth signaling pathways can extend longevity by 30-50% but also lower the incidence of age-related loss of function and disease, including tumors and neurodegeneration. Dietary restriction also increases healthspan and protects against diabetes, cancer, and cardiovascular disease in rhesus monkeys, and in humans it causes changes that protect against these age-related pathologies. However, although some forms of DR may be beneficial, this severe dietary regimen that induces major health benefits is not a desirable option for most people. Drugs that target nutrient-sensing pathways and mimic the effects of DR to obtain the health benefits of DR are more realistic, but before they can be considered for chronic administration they require large investments.

**Justification**

It is clear that the biomedical research has reached a point where interventions that function primarily on aging can be carefully proposed. Further progress requires informed discussion and debate on the best avenues for development to pursue, the risks involved, and how the success of proposed interventions can be measured. After discussions with many leaders in biogerontology, industry, and government funders, the organizers, have proposed the workshop described herein to develop realistic plans on how to move forward to identify interventions that can optimize healthspan.

**B. THE CHAIRS**

**Dr. Luigi Fontana** is Professor in the Department of Medicine at Salerno Medical School, Italy and at the Washington University Medical School in St.Louis, MO, USA and Associate Director of the Longevity Research Program of the Washington University Medical School in St.Louis.

**Dr. Donald Ingram** holds an academic appointment as Professor and Chief of the Nutritional Neuroscience and Aging Laboratory at the Pennington Biomedical Research Center in Baton Rouge, Louisiana, a component of the Louisiana State University System.

**Dr. Valter Longo** is presently the Director of the Longevity Institute and Edna Jones Chair Professor of Biogerontology at the University of Southern California.

**Local Organizer**

**Prof. Giampaolo Velo, M.D.**, has been Full Professor of Pharmacology and Head of Clinical Pharmacology Unit, at the University of Verona, Italy until October 2012. He is the Director of the Reference Centre for Education and Communication within the WHO Programme for International Drug Monitoring.
PROGRAM SCHEDULE AND PLANNING CONSIDERATIONS

We are proposing unique features that depart from the conventional organization of most scientific meetings. In the morning we will organize short 20-min talks followed by 10 minutes for questions to allow the experts to present relevant data, whereas at least 1 session in the afternoon will be devoted to discussion related to the morning session, to offer clear avenues to establish a plan on how to best translate these basic findings into clinical applications.

As described below, the venue in Erice, Sicily, provides an ideal facility and atmosphere for the workshop. There will be designated facilitators who will conduct the workshop and lead discussion. Participants will be instructed in advance to focus on the goals below. By the end of the conference we anticipate to have:

1) Identified the 5 most promising drug targets and the expected effect on aging and diseases
2) Described the drugs that target them or the need for the identification of additional drugs
3) Listed all of the known or potential side effects expected from chronic use of these drugs
4) Describe the clinical trials testing each category of drugs, even if they have been used for different disease treatment in humans (example, rapamycin for cancer).

The chairs will determine the interest by major journals in publishing the conference proceedings in the form of a didactic special issue of the journal.

Program
The meeting will begin on Tuesday October 8 in the evening with a Sicilian Typical Welcome. The scientific program will start on Wednesday October 9. Each session will feature 2 to 3 speakers (20 min/each + 10 min discussion). The latest draft of the scientific program is provided below.

TUESDAY, OCTOBER 8

Arrival of Participants

9.00 p.m.
Marsala and Sicilian Cakes at San Rocco’s Cellar

WEDNESDAY, OCTOBER 9
Session 1. Opening address, introduction and keynote presentation

9.00-9.15 a.m. Opening Address
Giampaolo Velo (University of Verona)

9.15-9.30 Introduction and purpose of the conference
Luigi Fontana (Washington University), Donald Ingram (Pennington Biomedical Research Center) and Valter Longo (University of Southern California)

Because the US National Institute on Aging has been so central in the funding of basic research leading to the major discoveries discussed by many of the participants but also because the NIA plays a central role in clinical trial related to drugs and interventions to protect the elderly, the Director of the Extramural Biology of Aging Division of the NIA has been asked to open the conference. He will provide an overview of what some of the major biogerontology discoveries have been but also about what are the major hurdles to overcome before we can consider pharmacological anti-aging strategies.

9.30-10.00 Keynote presentation:
Sierra, Felipe (NIA, NIH)

Model systems in drug discovery

Session 2. Targeting the GH/IGF-I pathway 1

The GH/IGF-I axis contains some of the best-studied pro-aging pathways. Session 2 will focus on the drugs and mutations that inhibit this pathway and on their effect on cellular protection and lifespan. Potential pitfalls will also be discussed.

Chairs: Manlio Vinciguerra & Adam Antebi

10.00-11.00 a.m.
Bartke, Andrzej (Southern Illinois University)
“Growth hormone, inflammation and insulin signaling”
Mitchell, Jay (Harvard)
“Translational Potential of Short Term Dietary Restriction”

11.00-11.30 Coffee break

11.30-12.30
Johnson, Thomas (University of Colorado)
“Identifying Critical Pathways to Slow Human Aging: Let the Genome Do the Talking”

Cynthia Kenyon (University of California San Francisco)
Screening for stress resistance and longevity drugs in human cells
Session 3. Calorie Restriction 1: Effects and mimetics
Calorie restriction is perhaps the most discussed pro-longevity intervention in history. Leaders in the field will discuss the pathways believed to be at the center of CR effects and the drugs developed or being developed with CR mimicking effects. Potential pitfalls will also be discussed.

Chairs: Rafael Decabo

12.30 -1.30 p.m.
Sinclair, David (Harvard)
“Advancing longevity-promoting molecules into the clinic”
Longo, Valter (University of Southern California)
Fasting Mimicking Diets and Healthspan

1.30-3.00 Lunch

Session 4. Calorie Restriction 2: Biomarkers and gene targets from calorie restriction studies

Chairs, Samuel Klein & Luigi Fontana

3.00-4.30 p.m.
Decabo, Rafael (National Institute on Aging)
“CR and CR mimetics; Where are we now?”
Donald, Ingram (Pennington Center)
“Mimicking Calorie Restriction by Putting Cells on a Diet”
Klein, Sam (Washington University)
“Metabolically normal and abnormal obesity”

4.30—5.00 Coffee break

5.00-6.00
Vijg, Jan (Albert Einstein College of Medicine)
“Genetic and epigenetic drift in aging”

Fontana, Luigi (Salerno & Washington University)
“Calorie restriction and disease in Humans”

6.00-7.00
Discussion on CR Mimetics
Fontana, Ingram, Longo, Decabo, Sinclair,
THURSDAY, OCTOBER 10

Session 5. Gene targets and biomarkers from centenarian studies
Centenarian studies are particularly important since many centenarians in addition to surviving 20 years more than average, often do not develop any chronic disease. Some of the leading experts will present on the genes and pathways believed to contribute to their ability to achieve optimal healthspan. Several speakers will also point to drugs being developed to target or affect these “longevity” genes. Potential pitfalls will also be discussed.

Chairs: Calogero Caruso & Donald Ingram

9.00-11.00 a.m.
Barzilai, Nir (Albert Einstein College of Medicine)
“Biomarkers for longevity of centenarians”
Franceschi, Claudio (University of Bologna)
“Inflamming and biomarkers of human aging: an OMICS approach”
Passarino, Giuseppe (Calabria University)
“The search of common genetic variability involved in human longevity: results and perspectives”
Suh, Yousin (Albert Einstein College of Medicine)
Mechanisms of Syringaresinol in Protection against Aging

11.00-11.30 Coffee Break

Session 6. Targeting the GH/IGF-I pathway 2

Chair: Tom Johnson

11.30 a.m.-12.30 p.m.
Kopchick (Ohio University)
“Growth Hormone Receptor Antagonists; Bottled Longevity”
Brown-Borg, Holly (University of North Dakota)
“Linking methionine metabolism to aging and longevity: Role of hormones and diet”

12.30-2.00 Lunch

Session 7. Tor - S6K signaling and autophagy
One of the major genetic pathway widely believed to have potential to be targeted in the near future to promote healthy aging is the Tor/S6K pathway. Leaders in the field will present on the effects of rapamycin on aging and/or diseases in both mice and humans and on the novel drugs being developed to target Tor/S6K. Because rapamycin is already being tested in human studies, some focus will be on
both its positive and its potentially negative effects during chronic use in humans. Potential pitfalls will also be discussed.

**Chair: Valter Longo & Andrzej Bartke**

2.00-3.30 p.m.  
**Kennedy, Brian (Buck Institute)**  
“Evaluating the TOR pathway as a target to extend healthspan”

**Antebi, Adam (Max Planck)**  
“Natural metabolites that enhance health and longevity”

**Curiel, Tyler (University of Texas San Antonio)**  
“Immune aspects of interventions to extend lifespan and healthspan”

3.30-4.30  
**Discussion on GHR/IGF-I and Tor-S6K drugs**  
Fontana, Ingram, Longo, Kopchick, Tyler, Kennedy

4.30 **Coffee and free time**

5.00-5:30  
**Discussion on novel target and biomarkers**  
Fontana, Ingram, Longo, Suh, Vijg

**FRIDAY, OCTOBER 11**

**Session 8. Epigenetics and regeneration**
Whereas CR can delay aging and prevent diseases, epigenetic interventions and regeneration have the potential to render an organism younger. Although we are still at the very beginning of this field of research, leading scientists have begun to unravel the connection between epigenetics, stem cell-based regeneration and aging. Potential pitfalls will also be discussed.

**Chairs: Brian Kennedy & David Sinclair**

9.00-10.00 a.m.  
**Brunet, Anne (Stanford)**  
“Epigenetic and metabolic regulation of aging”

**Madeo, Frank (University of Graz)**  
“Spermidine: A natural autophagy inducer and longevity elixir”

10.00-10:30 **Coffee break**

10.30-11.30
Rudolph, K.L. (Leibniz Institute for Age Research)
“Targeting p21 to improve stem cell functionality and regeneration during aging – from proof of concept to compound development”
Lepperdinger, Guenter (University of Innsbruck)
“NA”

11.30-12.00 Discussion

12.00-1.30 Lunch

Session 9. Novel drug targets
This session will be dedicated to some of the most promising research on novel drug targets and drugs with the potential to affect aging and healthspan. Potential pitfalls will also be discussed.

Chairs: Frank Madeo & Giampaolo Velo

1.30-3.30 p.m.
Sedivy, John (Brown University)
“Aging promotes global epigenetic changes leading to activation of transposable elements”
Spindler, Stephen (University of California, Riverside)
“Flies, mice and humans: Screening for compounds which extend healthy lifespan”
Gems, David (University College London)
“Host-microbiota interactions as a target for interventions that slow aging”
Shadel, Gerry (Yale)
“Epigenetic regulation of longevity via mitochondrial-stress signaling”

3.30-4.00 Coffee break

4.00-5.00 Discussion on Epigenetics/Regenerative and Other Drug targets
Fontana, Ingram, Longo, Madeo, Barzilai

5.00-6.00 Final Discussion and Conference Summary
Fontana, Ingram, Longo, Velo

8.00 p.m. Social Dinner

SATURDAY, OCTOBER 12
Field trip to Segesta’s Greek Temple and Theatre

SUNDAY, OCTOBER 13

Departure of Participants

E. CONFERENCE LOGISTICS

Conference site and facilities
The conference will be held in the Ettore Majorana Foundation and Centre For Scientific Culture, in Sicily, Italy. The Centre is situated in the old pre-mediaeval city of Erice where four restored monasteries (one of which was the residence of the Viceroy of Sicily during the XIV and XV Centuries) provide an appropriate setting for high intellectual endeavour. These ancient buildings are now named after great scientists and strong supporters of the ‘Ettore Majorana’ Centre. There are living quarters in for people attending the Meetings at the Centre. All conference sessions are plenary and will be held in one of the Lecture Halls of the Foundation. We will also use this area for coffee/tea breaks and there are other rooms, as well as the beautiful surrounding gardens, that are more than suitable for break-out activities. There is also disabled access to the “Paul A.M. Dirac” Hall in Patrick M.S. Blackett Institute (San Domenico Monasteri).

Conference Secretariat: Secretariat support for the Workshop will be provided by the School of Pharmacology of the Ettore Majorana Foundation and Centre For Scientific Culture in ERICE (Sicily), Italy (see enclosed letter from Prof. Giampaolo Velo). For any enquiry/problem, please contact Ms Angela Khuu (phone +39 045 8027505; mob. +39 3315858235; e-mail: angelasimona.khuu@gmail.com).

Speaker subsidies:
- Air travel: Round trip coach class airfares have been estimated for various geographical regions in the US as based on the information available to the travel agency.
- Accommodation: Lodging subsidy rooms at the Foundation or in partner hotels are provided for entire conference period, i.e., a maximum of 5 nights.
- Transportation: Transportation involves shuttle service from and to the Palermo or Trapani Airports.

Inclusion of women, minorities and persons with disabilities
The organizers have sought the best possible speakers in each session that would fit the aims and scope of the conference. We specifically considered women and minorities and asked our colleagues explicit advise in this respect. Whenever a female, handicapped or ethnic minority (for the US) was available this person was selected. This has resulted in a total of 5 women speakers. At the time of submission of this grant not all candidate speakers have been invited. We are still trying to increase the number of female and/or minority or handicapped speakers from the US. However, we feel that 5 female speakers out of a total of 40 invited speakers reflect the participation of women in this field reasonably well. The conference hall is accessible for the handicapped.
We would like to thank the following sponsors for helping to make this workshop possible:

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