Brussels, 17 May 2024

COST 032/24

DECISION

Subject: Memorandum of Understanding for the implementation of the COST Action "SENESCENCE2030: Targeting Cell Senescence to Prevent Age-Related Diseases" (SENESCENCE2030) CA23119

The COST Member Countries will find attached the Memorandum of Understanding for the COST Action SENESCENCE2030: Targeting Cell Senescence to Prevent Age-Related Diseases approved by the Committee of Senior Officials through written procedure on 17 May 2024.

MEMORANDUM OF UNDERSTANDING

For the implementation of a COST Action designated as

COST Action CA23119
SENESCENCE2030: TARGETING CELL SENESCENCE TO PREVENT AGE-RELATED DISEASES (SENESCENCE2030)

The COST Members through the present Memorandum of Understanding (MoU) wish to undertake joint activities of mutual interest and declare their common intention to participate in the COST Action, referred to above and described in the Technical Annex of this MoU.

The Action will be carried out in accordance with the set of COST Implementation Rules approved by the Committee of Senior Officials (CSO), or any document amending or replacing them.

The main aim and objective of the Action is to The aim and objective of SENESCENCE2030 is to create and maintain a synergetic and multidisciplinary network of academics, researchers and clinicians working to advance the understanding of cellular senescence and its interaction with aging, to improve well-being in aging populations worldwide, through the specific objectives detailed in the Technical Annex.. This will be achieved through the specific objectives detailed in the Technical Annex.

The present MoU enters into force on the date of the approval of the COST Action by the CSO.

OVERVIEW

Summary
Preventing or alleviating aging associated diseases, collectively rather than individually, is the challenge to extend the human healthspan.

The knowledge on cellular and molecular mechanisms identified so far as "hallmarks of aging" allow experimental strategies to prevent aging anticipation and extend the healthspan. A body of evidence indicate that cell senescence is a targetable hallmark of aging, typically associated with metabolic disorders, cardiovascular diseases, neurodegeneration and cancer.

The Action SENESCENCE2030 aims at rooting in Europe the vision of cells senescence and its targeting at center for the prevention of aging related disorders.

Through the engagement with international partners, SENESCENCE2030 generates an interdisciplinary and intersectoral network of experts in geroscience and senescence, facilitating the acquisition of new skills and knowledge among young researchers, medical personnel and innovators from Inclusiveness Target Countries.

SENESCENCE2030 goes beyond the state-of-the-art by opening vibrant knowledge exchange on senescence and senotherapy, trying to overcome the difficulties that prevent in Europe the clinical application of these knowledge for the identification of feasible diagnostics paths, more efficient clinical trials, and effective interventions on lifestyle and nutrition.

SENESCENCE2030 will highlight the socio-economic impact of therapeutic approaches and cost-effectiveness of timing interventions to define innovative processes, measures and products of impact on industries, funders and policy makers interested in addressing healthcare and socioeconomic challenges related to the aging.

Overall, SENESCENCE2030 will empower the transition from a disease-centered therapeutic approach to a balanced preventive and personalized treatment to avoid aging anticipation and promote individuals healthspan extension for the next decade.

Areas of Expertise Relevant for the Action	**Keywords**
● Biological sciences: Cell signalling and cellular interactions ● Basic medicine: Metabolism, biological basis of metabolism related disorders ● Clinical medicine: Non-communicable diseases	● ageing ● healthspan ● gero-diagnostic ● senotherapies ● cell senescence

Specific Objectives
To achieve the main objective described in this MoU, the following specific objectives shall be accomplished:

Research Coordination
● RCO1 Advancing Comprehensive Knowledge of Cell Senescence identifying knowledge gaps, emerging

trends, and potential areas for further exploration of cell senescence in relation to human aging, through networking meetings, training schools, STSMs, surveys of the scientific literature, and production of collaborative strategic documents and scientific publications.
● RCO2 Integrating Multi-Omic Approaches including genomics, transcriptomics, proteomics, epigenomics, microbiomics and single-cell analytic tools by sharing clinical and basic research data sets, fostering joint research initiatives.
● RCO3 Understanding Senescence Heterogeneity in different organs, developmental stages, environmental exposures and individual variations.
● RCO4 Promoting development of in Vivo Biomarkers for Senescence Detection to homogenize and enhance the accuracy of senescence analysis, and establish standardized and reliable in vivo senescence biomarkers for early detection and intervention strategies.
● RCO5 Exploring Novel Opportunities for Healthy Aging including but not limiting to senotherapeutics, lifestyle interventions, nutraceuticals, and synergies between the above.

Capacity Building
● CBO1 Research and Clinical Applications:SENESCENCE2030 will promote a pioneering platform for data exchanges in Europe, instrumental to address common mechanisms of age-associated diseases. The Action will enable the development of innovative measures and policy approaches, and facilitate the acquisition of new skills among young researchers, medical personnel and innovators.
● CBO2 Regulatory Bodies, Industry, and EU Entities: SENESCENCE2030 will establish an open communication platform,fostering dialogue and promoting timely approval and implementation of novel interventions.The platform will disseminate outcomes of RCO5 through the Action's website and social media channels to actively engage Regulatory Agencies, Industries and EU Entities in constructive dialogues.
● CBO3 Educational Outreach and Public Awareness: SENESCENCE2030 will enhance public awareness of senescence mechanisms and their significance in healthy aging to empower individuals to make informed decisions through training workshops, publications, dedicated sections on the Action's website, social media channels, participation in initiatives such as "The European Researchers' Night."
● CB04 Capacity Building and Training: SENESCENCE2030 will nurture a new generation of young professionals by facilitating knowledge transfer and skill development through training schools, exchange programs, Short-Term Scientific Missions (STSM), and supporting doctoral and postdoctoral training by promoting access to MSCA initiatives.
● CBO5 Ethical and Social Considerations: SENESCENCE2030 will proactively address concerns, including ethical, legal and socio-economic implications that may arise from advancements in cellular senescence research.

TECHNICAL ANNEX

1. S&T EXCELLENCE

1.1. SOUNDNESS OF THE CHALLENGE

1.1.1. DESCRIPTION OF THE STATE OF THE ART

Molecular characterization of mammalian senescent cells, the multiform function of the senescent cell secretome, cell senescence and the hallmarks of aging

In a ground-breaking paper published in 1961, Hayflick and Moorhead observed that *in-vitro* cultivated human fibroblasts had limited expansion ability after a certain number of passages while remaining alive and metabolically active[1]. This finding led them to postulate that limited proliferative potential (later dubbed the Hayflick Limit) could be a crucial component of organismal aging. Subsequent research established that telomere shortening, a phenomenon discovered in the cyliates by Elizabeth Blackburn and collegues[2] is responsible for limited replicative lifespans in primary mammalian cells[3], thus confirm the original postulate of Hayflick and Moorhead. However, given the experimental environment mainly based on *in-vitro* cultured cells, establishing a direct mechanistic link between cell senescence and body aging proved challenging. Moreover, the role of cell senescence in age-related disease etiology, if any, remained elusive.

The discovery that lifespan is controlled by genetic pathways and biochemical processes conserved in evolution, in organisms such as worms, yeasts, and flies, has significantly contributed to advancements in aging research over the past ten to fifteen years[4 5 6]. Furthermore, the development of mouse mutants, such as lines enabling the identification or manipulation of senescent cells[7 8] and various mouse models of aging[9] have accelerated the pace of discovery. Additionally, new experimental tools such as protocols for ex-vivo omic analysis of single cells have also played a major role in advancing the field.

Recent reviews have highlighted the crucial role that cell senescence plays in the aging process [10 11 12]. Altered persistence of senescent cells is specifically observed in chronic inflammation as well as in a number of other age-related diseases such as musculoskeletal dysfunctions (including osteoarthritis, osteoporosis and sarcopenia), fibrosis, neurodegeneration (including Alzheimer's and Parkinson's diseases), cancer and diabetes[13]. However, senescent cells are not solely responsible for aging. They also provide beneficial functions such as activating tumor suppressing mechanisms that limit the growth of potentially oncogenic cells[14 15], as well as playing critical roles during embryogenesis[16] and tissue remodeling, which includes wound healing[8].

The findings reported above align with the evolutionary hypothesis of antagonistic pleiotropy of cell senescence predicting that processes benefiting young organisms (such as suppressing cancer) may have detrimental effects in post-reproductive life and contribute to aging [17 18]. This dual role suggests a complex biology for senescent cells and their interactions with the environment, particularly with surrounding tissue microenvironments.

A significant milestone in understanding senescence mechanisms has been the discovery that senescent cells may secrete a large number of molecules, a phenomenon referred to as the senescence-associated secretory phenotype or SASP[19]. The SASP secretome includes pro-inflammatory cytokines, chemokines, extracellular matrix proteases and growth factors. Depending on the context, the secretome can be modulated in different ways to achieve different objectives, such as reinforcing senescence through autocrine mechanisms, spreading cellular senescent phenotypes paracrinally, or even activating immune responses against senescent cells[17].

In 2013, a set of common aging hallmarks across various organisms was proposed to the scientific community[20]. These hallmarks met three conditions: 1) their manifestation was age-associated, 2) experimentally accentuating their manifestation resulted in acceleration of aging, 3) they offered opportunities to decelerate, stop, or reverse aging by therapeutic interventions on them. So far, twelve hallmarks of aging have been identified, including genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, disabled macroautophagy, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, chronic inflammation, and dysbiosis[21].

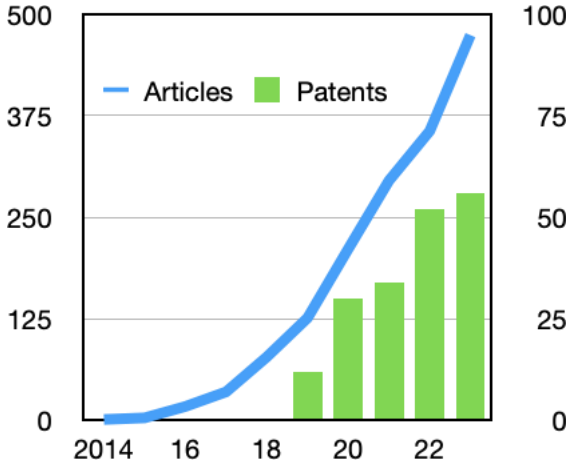
These hallmarks are functionally interconnected and drive the pathophysiology of many chronic disorders directly affecting disease development[22]. Interventions targeting any one hallmark may also target the others, preventing or alleviating multiple age-related diseases collectively rather than

individually[13]. Among these hallmarks, cell senescence is a key research focus for preventing, delaying, or alleviating age-associated diseases such as multiple metabolic disorders[23]. Research has shown that senescent cells are involved in maintaining cardiovascular health[24] which, in turn is a prerequisite for extended healthspan (the period of life spent in good health, free from chronic diseases and disabilities of aging).

The gold rush to senotherapies, lifestyle interventions, and prevention

After discovering the close association between cellular senescence and aging, including its connection to age-related diseases, it became reasonable to develop experimental strategies targeting senescent cells to prevent or delay tissue dysfunction and extend healthspan[7]. Current strategies, known as *senotherapeutics*, focus on developing molecules to specifically eliminate senescent cells (*senolytics*) or inhibit their SASP (*senomorphics*)[13] [11].

The field of senotherapy is experiencing significant growth, evidenced by data from PubMed scientific publications and the global database of patents. The search query used in both cases included variations of senolyt*, senother*, or senomor* in the record text. In 2015, only three articles related to senotherapy keywords were published. However, this number has been steadily increasing and is expected to reach nearly 500 papers by the end of 2023. Similarly, the number of published patents related to senotherapy has also increased. These patents encompass various potential applications, including preventing or curing diseases such as viral respiratory infections, Parkinson's disease, intervertebral disc deterioration, cancer, and more. Additionally, there are patents defining regimens useful in preventing/delaying the typical signs of aging and others establishing materials and methods for determining biological age by measuring parameters related to cell senescence. Other patents claim effectiveness in cosmetic treatments and define regimens for preventing or delaying signs of aging.



Despite cellular senescence's complexity and our limited understanding of its mechanisms and and functions[12], several clinical trials are showing promising results[25] [26]. These trials are important steps towards assessing the efficacy and safety of senolytics in human subjects.

A new industry sector is rapidly growing, exploring cellular hallmarks of senescence with a focus on cellular processes. A comprehensive list of companies in this field, currently comprising 180 entities, predominantly based in the United States, can be found at https://agingbiotech.info/companies/. Notably, the rapidly expanding industrial segment of Longevity Biotechnology Companies deserves special attention due to the related regulatory challenges: these companies are dedicated to developing interventions aimed at extending human healthy lifespan and, to some extent, also the overall lifespan[27].

At the same time, the literature on healthy diets, regular physical activity, and stress responses continues to grow as well. Numerous studies highlight the role of cell senescence in these mechanisms [28] [29] [30] [31] [32]. Therefore, not only pharmaceutical treatments but also the - much less regulated - field of lifestyle interventions increasingly benefit from understanding cell senescence mechanisms.

Furthermore, recent literature reveals that social factors like low socioeconomic status, adverse life events, and unfavourable psychological states significantly impact aging variability. Researchers have started to examine the associations between these "social hallmarks of aging" and various biological indicators[33]. The aim of research on social hallmarks is to illuminate the connections between social and biological factors and their impact on health outcomes. For example, one study found a link between occupational characteristics and accelerated biological aging[34], while another study suggested that education levels may slow down this process, as shown by DNA methylation patterns in individuals of European descent[35].

A transition from a disease-centred medical R&D system to a balanced preventive and personalized treatment healthcare system has recently been advocated to reduce social inequalities in health and achieve sustainable universal healthcare coverage[36].

1.1.2. DESCRIPTION OF THE CHALLENGE (MAIN AIM)

Despite significant advances of research in cellular aging over the past 50 years, our comprehension and mastery remain limited. The mechanism(s) originating cell senescence remain poorly understood:

recent puzzling discoveries shed light on the activation, under certain circumstances, of an endogenous retrovirus normally dormant in the genome[37]. Other areas of intense research are actively studying the interactions between cell senescence with other hallmarks of aging as well as investigating specific biomarkers associated with subtypes of senescent cells.

At the same time, researchers are investigating the potential of targeting senescent cells, not only for the treatment of age-related diseases but also for the extension of healthspan, and potentially even lifespan. This research field is attracting growing interest from investors, particularly in the USA, as well as increasing worldwide media coverage. As an example, in the September 30, 2023, issue of The Economist magazine, their Technology Quarterly was dedicated to "Longevity."

However, it is important to note that cellular senescence is a natural part of organism development and aging. Therefore, it is advisable to adopt a cautious approach to the potential side effects of senolytics and senomorphics, as these have been shown to have dose-dependent effects in clinical trials and off-label use. Furthermore, given that cellular senescence is a lifelong phenomenon, personalized preventive approaches based on senotherapies as well as on lifestyle, diet, and nutraceuticals need to be considered, even in the absence of any diseases: this requires both new regulatory approaches to clinical development and measures against misleading claims of efficacy[27] [26].

The implementation of senotherapeutics, targeting senescent cells in healthy organs or even healthy individuals, and the promotion of senescence-preventing lifestyles both pose several scientific, logistical, and regulatory challenges. Some of these obstacles are dependent on advancements in knowledge, others are related to the need for more efficient clinical trials, while others require improvements in education, public perception, and public funding. Addressing these challenges necessitates adopting multidisciplinary, multisectoral approaches, and fostering collaboration among experts.

Addressing these challenges and uncertainties is at the core of the Action.

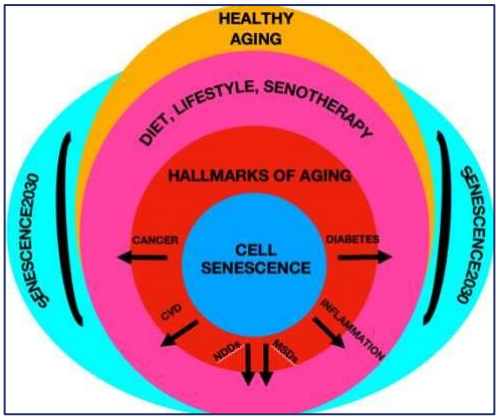
The aim and objective of SENESCENCE2030 is to create and maintain a synergetic and multidisciplinary network of academics, researchers and clinicians working to advance the understanding of cellular senescence and its interaction with aging, to improve well-being in aging populations worldwide. SENESCENCE2030 aims to advance the understanding of cellular senescence and its interactions with other aging processes, paving the way for innovative and safe interventions. SENESCENCE2030 will crucially contribute to deeply root in Europe the new vision positioning cell senescence at centre of pathogenesis of different age-related disorders. The project will contribute to the progress of knowledge as well as to the establishment of evidence-based practices, improved regulatory frameworks, and the dissemination of accurate information to the public and healthcare professionals. By tackling these objectives head-on, SENESCENCE2030 strives to unlock the full potential of cellular senescence research in improving quality of life for individuals as they age.

In the last decade, the World Health Organization highlighted global challenges regarding health and aging[38]. The number of people aged 60 years or older is predicted to increase from 900 million to 2 billion between 2015 and 2050. This rapid population aging has led to numerous socioeconomic burdens associated to age-related disabilities, including sensory impairments, back and neck pain, hearth disease, chronic obstructive pulmonary disease, depressive disorders, falls, diabetes, dementia and osteoarthritis. Notably, heart disease, stroke, and chronic lung disease are identified as the primary causes of mortality among older individuals. These facts led to the adoption of United Nations Resolution 75/131 dedicating the decade from 2020 to 2030 to aging. Their action plan promotes 10 years of sustained collaboration promoting research, data exchange, and innovation in coping with an aging population.

Cellular senescence research has the potential to significantly address the socio-economic challenges outlined by WHO and UN Resolution 75/131, recent studies suggest that society can benefit economically from improving how we age: extending US life expectancy by one year could be worth US$ 38 trillion[39]. The main aim of SENESCENCE2030 is to contribute to the full realization of this potential.

1.2. PROGRESS BEYOND THE STATE-OF-THE-ART

1.2.1. APPROACH TO THE CHALLENGE AND PROGRESS BEYOND THE STATE OF THE ART



The accompanying graphical abstract depicts SENESCENCE2030's proposal to investigate and mitigate - through optimal combinations of diet, lifestyle and senotherapies - the buildup of senescent cells, which play a pivotal role in the progression of prevalent age-related diseases such as cancer, diabetes, inflammation, cardiovascular (CVD), neurodegenerative (NDD) and musculoskeletal (MSD) diseases, with their socio-economic impact.

Through an interdisciplinary, intersectoral approach and active engagement with international partners, SENESCENCE2030 is focused on the development of radically innovative strategies and solutions that enhance the well-being and quality of life for aging populations worldwide.

At the same time, SENESCENCE2030 will serve as a complementary and integrated initiative, synergizing with existing efforts that may have limitations due to their specific focus on a certain topic, approach, geography, or sector.

SENESCENCE2030 aligns with the growing recognition of the importance of tackling aging-related challenges and provides a unique opportunity to address the socioeconomic implications of an aging global population. The project will go beyond the state-of-the-art, leading the way in advancing knowledge, research, and strategies related to cellular senescence and healthy aging through a combination of the following approaches.

Empowering Knowledge SENESCENCE2030 aims to advance both fundamental and translational research on senescence, enhancing the understanding of which tissues, disease or conditions might benefit more from the management of cell senescence. Findings will be disseminated through thematic publications, a dedicated web site connected to social networks, and workshops, contributing to the global knowledge base in this crucial area.

Bridging the Gap By fostering meaningful interactions between clinicians and basic scientists, SENESCENCE2030 seeks to establish a strong commitment to identifying useful senescence biomarkers and feasible diagnostic paths for the early detection of frailty and age-related disorders. This collaborative effort will bridge the gap between research and clinical practice, enhancing early intervention and targeted therapeutic approaches.

Optimizing Study Designs SENESCENCE2030 will provide new recommendations for the study design of effective gerodiagnostics and clinical trials. A very unique feature of our proposal is to focus on whether, when through the human lifespan and how pharmacological, lifestyle or combined treatments should be most properly considered from both a clinical and a cost-effectiveness perspective. By optimizing research methodologies and protocols, we aim to accelerate the development of evidence-based interventions for aging-related challenges.

Promoting Healthy Aging Through evidence-based recommendations and strategies, SENESCENCE2030 will contribute to preventing, delaying, or attenuating age-related tissue and organ dysfunctions. We plan to actively open a dialog with regulatory bodies to foster translation of scientific evidence into clinical practice and decrease the current gap between North America and EU in this area. Our focus on promoting healthy aging will be a pivotal step in improving the overall quality of life for aging populations.

Discouraging Misleading Practices SENESCENCE2030 will take a proactive stance by advising against exaggerated anti-aging claims and unreasonable for-profit activities. Our aim is to ensure that any advancements or interventions are grounded in sound science and ethics.

Comprehensive Policy Impact Evaluation Studies SENESCENCE2030 aims to actively support initiatives that delve into policy impact evaluation studies. These studies will assess the effects of fundamental and translational research on senescence, not just from the perspective of the average effect on the representative patient (the average effect) but also by considering the comprehensive distributional effects that may occur within a population (distributional effects). We seek to gain a deeper understanding of the diverse impacts that senescence research can have on different individuals, demographics, and social groups.

Driving Systemic Change SENESCENCE2030 will identify pragmatic solutions to impact educational

and public health systems, as well as the industry and regulatory agencies, promoting a new vision of the aging process. By driving systemic change, we strive to create a more age-inclusive and supportive environment for older individuals.

1.2.2. OBJECTIVES

In the following paragraphs, the overarching objective of SENESCENCE2030 is dissected into specific, measurable, achievable, and relevant issues, to detail with improved clarity and precision each specific objective.

1.2.2.1. Research Coordination Objectives

RCO1 Advancing Comprehensive Knowledge of Cell Senescence: SENESCENCE2030 will produce an interdisciplinary collaborative effort to identify knowledge gaps, emerging trends, and potential areas for further exploration of cell senescence in relation to human aging. This will be achieved through:

- Networking meetings and STSMs
- Surveys of scientific literature
- Collaborative strategic documents and scientific publications.

RCO2 Integrating Multi-Omic Approaches: Collaborations will be promoted between individual laboratories participating in SENESCENCE2030 in adopting omic approaches (including genomics, transcriptomics, proteomics, epigenomics, microbiomics and single-cell analytic tools) aiming at:

- Sharing clinical and basic research data sets and facilities from SENESCENCE2030 participating Institutions also by supporting joint research initiatives.
- Fostering joint research initiatives in response to further European calls.
- Explore opportunities of potential collaborations with large endeavors at the international level, such as the SenNet initiative.

RCO3 Understanding Senescence Heterogeneity: coordinate research and share data on the fundamental heterogeneity of senescent cells in various contexts, including different organs, developmental stages, environmental exposures, and individual variations. This objective aims at:

- Gain insights into the distinctive roles of senescent cells in human aging and disease.
- Propose more precise intervention strategies with clinically meaningful benefits compared to currently available opportunities.
- Device novel therapeutic targets in senescence mechanisms to be further considered by European industries.

RCO4 Developing In Vivo Biomarkers for Senescence Detection: Identify in vivo biomarkers based on the knowledge gained from SENESCENCE2030 research. These biomarkers will facilitate the assessment of senescence in diverse contexts with the following objectives.

- Homogenize and enhance the accuracy of senescence analysis and assessment within SENESCENCE2030 participating laboratories and hospitals.
- Establish standardized and reliable in vivo senescence biomarkers for early detection and intervention strategies.
- Device diagnostic products or processes amenable to further development by the European industry.

RCO5 Exploring Novel Opportunities for Healthy Aging: SENESCENCE2030 will produce timely, authoritative reviews of interventions targeting cellular senescence at different times through human life. This effort will include (but not limited to):

- senotherapeutics,
- lifestyle interventions,
- nutraceuticals,
- synergies between the above

In pursuing this objective, particular attention will be dedicated to whether, when throughout the human lifespan and how to use the above treatment strategies. A critical component of Senescent2030 reviews will involve analyzing the perspectives and stances of various regulatory bodies on this matter.

1.2.2.2. Capacity-building Objectives

CBO1 Bridging Research and Clinical Applications. Leveraging its interdisciplinary network SENESCENCE2030 will establish a pioneering platform for data exchanges in Europe. This platform will serve as a hub for further studies with the following primary aims:

- Foster vibrant knowledge exchange and collaboration between basic researchers and healthcare professionals specializing in cell senescence-based approaches. This collaboration will be instrumental to effectively address common mechanisms of age-associated diseases.
- Enable the development of innovative measures, encompassing products, processes, services, organizational methods, or policy approaches. These measures, informed by advanced scientific knowledge, will aim at proactively prevent age-associated diseases and address critical healthcare challenges for the aging population.
- Facilitate the acquisition of new skills, especially among young researchers, medical personnel and innovators from Inclusiveness Target Countries and Near Neighbour Countries (refer also to CBO4).

CBO2 Regulatory Bodies, Industry, and EU Entities: In the context of its Communication, Dissemination, and Valorization Strategy, SENESCENCE2030 will promote an open communication platform dedicated at fostering dialogue and promoting development, timely approval, and implementation of novel interventions in Europe. These interventions include systemic approaches to research on cell senescence as well as senotherapeutics adoption, healthy lifestyle promotion, and the deployment of combined prevention/treatment strategies at optimal stages throughout the human lifespan. The platform will harness the outcomes of RCO5 and disseminate them through the Action's website and social media channels. In addition, the platform will actively engage in constructive dialogues with the following stakeholders:

- Regulatory Agencies: This includes collaborating with organizations such as the European Medicines Agency and medicines regulatory authorities within EU Member States. SENESCENCE2030 will engage with Health Technology Assessment (HTA) bodies, including the recently established European Network for Health Technology Assessment (EUnetHTA 21) consortium.
- Industry: SENESCENCE2030 engagement will be extended to single companies, with a particular focus on small and medium-sized enterprises (SMEs), as well as public and private financial investment agencies. It will also seek collaboration with industry associations, such as those included under the Innovative Health Initiative umbrella.
- EU Entities: SENESCENCE2030 will actively connect with EU bodies capable to promote "systemic" initiatives in fields relevant to the Action. Institutional contacts will include High-Level Advisory Boards and key figures associated with the European Council of Innovation and the European Institute of Technology (Health EIT, in particular). Furthermore, the Action will seek collaborations with European Research Infrastructure Consortia such as Euro-BioImaging, ECRIN and BBMRI.

This objective is particularly innovative in Europe, where regulatory bodies and EU R&D programs are not yet as explicit in the field as their North-American counterparts.

CBO3 Educational Outreach and Public Awareness: SENESCENCE2030 is committed to enhance public awareness of senescence mechanisms and their significance in healthy aging. This objective will be achieved by disseminating accurate information, addressing misconcepts, and empowering individuals to make informed decisions. SENESCENCE2030 will perform the following:

- Training Workshops and Publications for Educators: Senescence 2030 will organize specialized training workshops and create educational publications tailored for schoolteachers. These resources will provide educators with the knowledge and tools to effectively convey the importance of cellular senescence in the context of healthy aging and, consequently of healthy behaviors throughout the lifespan.
- Dedicated Sections on the Action's Website and Social Media Channels: These channels will serve as hubs for disseminating reliable information and engaging content, and updates related to cellular senescence and its implications for healthy aging.
- Participation in EU-wide Initiatives: Senescence 2030 will actively participate in larger European initiatives having similar objectives of bringing research and researchers closer to the public, such as "The European Researchers' Night." These Europe-wide public events, organized within the framework of the Marie Skłodowska-Curie Actions, provide an ideal platform to engage with the wider public and promote SENESCENCE2030's mission.

CB04 Capacity Building and Training:
The outcomes of research on cell senescence possess the potential to impact a diverse range of professionals, including researchers, innovators, medical professionals, nutritionists, and more. SENESCENCE2030 is deeply committed to nurturing a new generation of young professionals by facilitating knowledge transfer and skill development through the following initiatives.

- Training Schools: SENESCENCE2030 aims at establishing interdisciplinary and intersectoral environments through specialized training schools, which will provide a platform for acquiring new skills coupled with an advanced understanding of geroscience and its socio-economic implications.
- Exchange Programs: SENESCENCE2030 will facilitate exchange programs, including Short-Term Scientific Missions (STSM), designed to enable interdisciplinary, intersectoral knowledge sharing and collaboration. These programs will foster international collaboration and the expertises of participants in the field of cell senescence.
- Marie Skłodowska-Curie Actions (MSCA): SENESCENCE2030 will actively support opportunities for doctoral education and postdoctoral training under the auspices of the European Research Area. By promoting access to MSCA initiatives, the Action aims at empower early-career researchers with the resources and expertise needed to strive for excellence in the field of cell senescence.

Particular attention will be taken to ensure continuity of the achievements also after the end of the Action.

CBO5 Ethical and Social Considerations: SENESCENCE2030 is dedicated to proactively address concerns, including ethical, legal and socio-economic implications that may arise from advancements in cellular senescence research (see also CBO3). This objective will be pursued by

- fostering interdisciplinary discussions to ensure that research and applications align with ethical and juridical principles and societal values.
- evaluating the socio-economic implications of interventions focusing on healthy aging (see RCO5), considering that cost-effectiveness of different intervention strategies (eg. senotherapeutics vs. lifestyle or combined) which may vary at different stages in human lifespan and in different social contexts.

2. NETWORKING EXCELLENCE

2.1. ADDED VALUE OF NETWORKING IN S&T EXCELLENCE

2.1.1. ADDED VALUE IN RELATION TO EXISTING EFFORTS AT EUROPEAN AND/OR INTERNATIONAL LEVEL

A comprehensive analysis of existing European and international research efforts related to cellular senescence reveals both promising achievements and areas where a systemic approach is lacking.

Within the European research landscape, a search of the CORDIS database identified 20 projects currently active in the field of cellular senescence. These involve in-depth basic research activities or deal with the study of senescent cells in the context of specific disease, and excellent individual research activities on cell senescence are funded by the European Research Council. However, there is a notable absence in the CORDIS database of systemic approaches that bridge the gap between biological sciences, medical/health sciences and social and human sciences. Furthermore, no call specifically addressing this promising field is currently available in the Funding & Tender Opportunities Portal or the Work Programmes of Horizon Europe for the years 2023-2024.

At the international level, various initiatives are working on systemic approaches to cellular senescence, research promotion, cooperation, and information exchange. Most notably, the NIH Common Fund's Cellular Senescence Network (SenNet) Program in the USA has recently invested about $190 million to create four-dimensional atlases of senescent cells throughout life and tissues[40]. Additionally, the business-oriented Longevity Biotechnology Association (www.longevitybiotech.org) and the science-based International Cell Senescence Association (ICSA www.cellsenescence.info www.icsa2022groningen.nl) have established significant presences in the field.

Notably, many research projects related to aging in a broader context are funded under Horizon 2020 and Horizon Europe, as well as by Joint Programming Initiatives within the ERAnet policies. Furthermore, the word "aging" is associated with several dozen actions in the COST database, with more than 22 of them currently active (while none is specifically dedicated to the cell senescence field).

Therefore, SENESCENCE2030 presents a unique and fundamental added value compared to existing European efforts. As a Pan-European Network with international projections, it gathers diverse expertise spanning biological, medical, and socio-economic fields, and includes representatives from academia, health systems, and business. Establishing positive synergies with existing European initiatives is a major objective of SENESCENCE2030, which will be accomplished through knowledge dissemination,

invitations to join Working Groups, and proposals for joint efforts where appropriate.

2.2. ADDED VALUE OF NETWORKING IN IMPACT

2.2.1. SECURING THE CRITICAL MASS, EXPERTISE AND GEOGRAPHICAL BALANCE WITHIN THE COST MEMBERS AND BEYOND

SENESCENCE2030 originated from a geographically well-balanced group of researchers,

The initial proposers formed a robust and interdisciplinary network comprising:

- Research teams with specific expertise in senescence hallmarks and their implications on age-related diseases.
- Clinical researchers from renowned research hospitals, dedicated to developing gerodiagnostic pathways, utilizing biomarkers for early diagnosis and risk prevention of frailty and age-related disorders, and conducting pioneering senotherapy clinical trials in Europe.
- Experts in medicinal chemistry and drug development, some with a history of collaboration with SMEs and industry.
- Economists, econometricians, statistics experts and sociologists specialized in health-related problems.
- Experts studying the molecular and cellular mechanisms through which diets and lifestyles influence health maintenance.
- Entrepreneurs involved in the development of senotherapy-related products, as well as representatives from relevant industry associations.
- Members of patient associations actively engaged in the field of age-associated diseases

At the same time, SENESCENCE2030 emphasizes openness and inclusivity to effectively fulfill its mission and policy. Efforts will be made to involve Young Researchers and Innovators (YRIs), ensuring a balanced gender representation throughout its duration. The Action will actively seek to expand its critical mass of experts,. Specific activities, as detailed in the following sections, will focus on engaging experts from industry sectors and regulatory bodies through stakeholder plans and brokerage events. This approach ensures a comprehensive and impactful network, bringing together diverse perspectives and experiences to address the challenges of cellular senescence and aging effectively.

2.2.2. INVOLVEMENT OF STAKEHOLDERS

To ensure a well-rounded approach, SENESCENCE2030 will actively engage with a diverse range of stakeholders. In the initial phase, the Management Committee will develop a strategic document dedicated to stakeholder engagement, which will be regularly updated annually. This document will prioritize geographical, gender, and YRIs balance to ensure long-term sustainability and effectiveness. It will also outline specific stakeholders whose targeting will be prioritized throughout SENESCENCE2030 program life, based on the general Action Plan.

By involving a wide range of stakeholders, SENESCENCE2030 aims to create a comprehensive and impactful network, amplifying its research outcomes and promoting societal benefits deriving from cellular senescence research. Stakeholder participation will be integrated into the SENESCENCE2030 annual conferences through relevant sections where stakeholders will be invited to contribute and interact. The following stakeholder categories will be considered:

Academic Community: Researchers will be invited to join SENESCENCE2030 to improve knowledge generation, data exchange, and technological advancements in cellular senescence research.

Medical and Health Sector: SENESCENCE2030 will actively engage with stakeholders in the medical and health sector, particularly those involved in age-related diseases, to disseminate the Action's vision and outputs to the sector while receiving valuable expertise, input, and feedback.

Industry: Given the growing significance of senotherapy in the industrial sector and the potential gap with North American and Asian countries, SENESCENCE2030 will actively foster engagement with industry, especially with Small and Medium-sized Enterprises (SMEs). The Action will invite industry representatives to its events and consider participation in industry-driven events for vision dissemination.

Young Researchers and Innovators, and Gender Balance: A dedicated section in the SENESCENCE2030 Strategic Document and its annual updates will focus on gender balance and career development for Young Researchers and Innovators;. SENESCENCE2030 members who are YRIs will actively participate in capacity building events, management structures, and decision-making

processes. Training schools and Short-Term Scientific Missions will benefit students and postdocs, fostering their cross-disciplinary expertise and career prospects in different sectors.

General Public: SENESCENCE2030 recognizes the potential enormous impact of its research on the general public. The Action will support public information and education initiatives about the significance and impact of cellular senescence research, with a special focus on patients.

Funders and Policy Makers: This critical stakeholder group will receive regular invitations to SENESCENCE2030 events. Position papers and explanatory documents on the project's outcomes will be sent to distinguished recipients, including high-level Advisory Groups of the European Commission and national/regional regulatory agencies.

Complementary Programs and COST Actions: SENESCENCE2030 will actively reach out to other European initiatives, in particular COST Actions, inviting their participants to join its structure and engage in networking events, training schools, and workshops. The aim is to disseminate new knowledge on cellular senescence and obtain valuable insights from other initiatives, reinforcing collaborative efforts and knowledge translation.

3. IMPACT

3.1. IMPACT TO SCIENCE, SOCIETY AND COMPETITIVENESS, AND POTENTIAL FOR INNOVATION/BREAK-THROUGHS

3.1.1. SCIENTIFIC, TECHNOLOGICAL, AND/OR SOCIOECONOMIC IMPACTS (INCLUDING POTENTIAL INNOVATIONS AND/OR BREAKTHROUGHS)

Several potential innovations and breakthroughs can be anticipated within the four years' timeline of the current proposal:

Potential Breakthroughs

- Identification and characterization of Senescent Cell modulators, paving the way for targeted interventions to manipulate senescence.
- Discovery of new diagnostic markers and technologies for the assessment of cell senescence, facilitating early detection and intervention in age-related conditions.
- Identification and characterization of potential targets for senescence intervention, providing new avenues for preventive measures and therapeutic interventions.

Potential Innovations

- New, science supported concepts related to healthy diets and life-styles, their potential impact on aging leading to innovations in the food, nutrition, fitness industry.
- Development of validated knowledge tools for characterizing Senescent Cells and senescence-associated secretory molecules, enabling a comprehensive understanding of their functions and interactions.
- Development of new technologies for the industrial segment of Longevity Biotech, based on senescence research and its implications for healthlife.

However, the transfer of knowledge of senescent cell biology to new technologies and the development of protocols and products of socio-economic value is still in its infancy. Therefore, it is essential to consider a longer timeframe for the full impact of the proposed COST Action:

Long Term Breakthroughs

- Development of Senescent Cells-based diagnostics, enabling early detection and monitoring of age-related diseases.
- Identification, characterization, and deployment of effective senolytics, agents that induce apoptosis in senescent cells, offering new treatment strategies for age-related disorders.
- Identification and characterization of effective SASP inhibitors, leading to therapies that mitigate the negative effects of the senescence-associated secretory phenotype, promoting healthier aging

Long Term Innovations

- Identification of innovative diagnostic procedures for tissue senescence, enabling targeted therapies for specific age-related conditions.
- Early diagnosis of age-associated diseases, allowing for timely and more effective medical interventions.

- Development of preventive measures and interventions for age-associated diseases, promoting healthier aging and reducing disease burden.
- Advancement of new therapies for age-associated diseases, based on a deeper understanding of senescence and its impact on health.
- Significant impact on well-being and extended "health-span" by subgroup patients, improving the overall quality of life for aging populations.
- Mitigate inequalities in prevention and care of aging related diseases in Europe.

3.2. MEASURES TO MAXIMISE IMPACT

3.2.1. KNOWLEDGE CREATION, TRANSFER OF KNOWLEDGE AND CAREER DEVELOPMENT

Through the following strategic measures, SENESCENCE2030 will foster the creation and dissemination of knowledge, facilitate collaboration, and support career development in the geroscience research domain, ultimately maximizing the impact of the Action's outcomes.

Establishing an International Consortium: The Action will form a collaborative international consortium to mitigate the risks of academic or financial ambitions, incentives, and rivalries impeding the discovery and testing of geroscience interventions. By fostering cooperation and exchange of ideas among investigators, disciplines, and institutions, SENESCENCE2030 will promote a systemic approach to research in the field.

Promoting Applications for R&D Funding: SENESCENCE2030 will actively encourage researchers to apply for funding opportunities under Horizon Europe and other European Commission (EC)-funded R&D programs. Special focus will be directed towards the development of effective gerodiagnostics as primary outcomes of clinical trials and to support advancements in gerosciences

Providing Consensus-Based Recommendations: The Action will facilitate the generation of consensus-based recommendations to inform study design and International Classification of Diseases (ICD) codes for clinical states such as frailty, multimorbidity, or sarcopenia. These recommendations will enhance the standardization and comparability of research findings, contributing to the overall advancement of the field.

Promoting MSCA Actions for Geriatrician Training: SENESCENCE2030 will actively promote applications for Marie Skłodowska-Curie Actions (MSCA) aimed at training scientists/clinicians with expertise in basic or preclinical geroscience research or interventional clinical trials. By nurturing a new generation of skilled researchers, the Action will bolster the field's capacity to address age-related disorders effectively.

Establishing Collaborative Research Platforms: SENESCENCE2030 will create collaborative research platforms that facilitate data sharing, interdisciplinary interactions, and joint research projects. These platforms will promote seamless collaboration among experts from different disciplines and institutions, encouraging the integration of diverse perspectives and expertise. By breaking down traditional research silos, these platforms will accelerate the pace of knowledge creation and transfer within the Action, leading to more comprehensive and impactful research outcomes.

3.2.2. PLAN FOR DISSEMINATION AND/OR EXPLOITATION AND DIALOGUE WITH THE GENERAL PUBLIC OR POLICY

To maximize the dissemination, exploitation, and engagement with the general public and policy stakeholders, SENESCENCE2030 will implement the following strategic measures, central to its plan:

Identifying Common Pathogenetic Mechanisms: The Action will actively advocate for the recognition of possible common pathogenetic mechanisms underlying age-related disorders. By engaging with relevant stakeholders, including funding agencies and policy-makers, SENESCENCE2030 will advocate for increased funding opportunities and incentives specifically targeted towards gerosciences research. This advocacy will reinforce the importance of gerosciences in addressing age-related diseases and promoting healthy aging.

Providing Expert Advice to the General Public: SENESCENCE2030 will serve as a credible source of expert advice on the progress in gerosciences. Through various communication channels, the Action will disseminate accurate information to the general public, ensuring they are well-informed about the latest advancements in the field. Additionally, SENESCENCE2030 will play a crucial role in debunking

exaggerated "antiaging" claims and exposing profiteering activities, thereby promoting informed decision-making among the public.

Highlighting Socio-Economic Impact: The Action will actively communicate the socio-economic impact of geroscience interventions related to lifestyle modifications, natural products, or repurposed off-patent agents. By showcasing the potential benefits of these interventions in improving healthspan and reducing healthcare costs, SENESCENCE2030 will engage public stakeholders, companies, and entrepreneurs in supporting and investing in geroscience research.

Engaging Drug Regulatory Agencies: SENESCENCE2030 will serve as a valuable resource for drug regulatory agencies by providing organized expertise and insights into geroscience interventions. By offering a comprehensive reference source on the safety and efficacy of these interventions, the Action will facilitate a more efficient bench-to-bedside translation of geroscience discoveries, accelerating the development and approval of novel interventions for age-related disorders.

Collaborating with Policy-Makers: The Action will actively engage with policy-makers at the European and national levels. By sharing evidence-based recommendations and policy briefs, SENESCENCE2030 will contribute to the formulation of health policies that prioritize healthy aging and geroscience research. Through dialogues, workshops, and policy forums, the Action will foster collaboration between researchers and policy-makers, ensuring that geroscience insights inform strategic decision-making.

Exploitation and Technology Transfer: SENESCENCE2030 will actively explore avenues for technology transfer and exploitation of research findings. The Action will encourage the commercialization of geroscience innovations and facilitate partnerships between academia and industry. By fostering technology transfer, SENESCENCE2030 will enhance the practical application of geroscience discoveries, ultimately benefiting society and the economy.

4. IMPLEMENTATION

4.1. COHERENCE AND EFFECTIVENESS OF THE WORK PLAN

4.1.1. DESCRIPTION OF WORKING GROUPS, TASKS AND ACTIVITIES

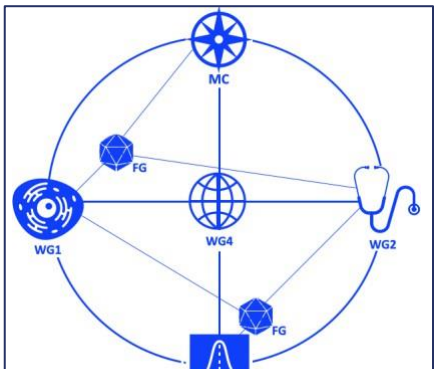
The Action activities will be overseen by the Management Committee (MC), the ultimate decision-making body of the network, led by the MC Chair and Vice Chair and composed of up to two representatives from each COST Member Country participating in the Action. The Action's MC will meet once a year in person, in conjunction with a main event (Workshop, Conference or Training School).

The Core Group (CG) - consisting of the Action Chair and the Action Vice Chair, WG leaders, Science Communicator, Short-Term Scientific Missions (STSM) Coordinator, Grant Awarding Coordinator (GAC), and Grant Holder Scientific Representative - will ensure that the steering decisions are discussed and prepared for the MC to meet the objectives of the Action. The CG will meet twice a year or more frequently if necessary.

A STSM Committee will implement the participation of Young Researchers in the Action and will be broadening geographical inclusiveness. The Action's Science Communicator will act as the main contact point for both Action participants and external parties for questions on Action communication, dissemination and valorisation.

Gender balance as well as involvement of YRIs and participants from ITCs will be considered in the constitution of the CG, MC, WG leaders, STSM coordinator and Science Communicator. At least one YRIs will be WG leader, and at least another will be Science Communicator or STSM Coordinator.

To optimize interdisciplinary and cross-sector interactions, as depicted in the figure, a streamlined structure with a limited



number of four working groups is proposed. In addition, highly flexible structural components are also anticipated in the form of special Focus Groups spun out of WGs, to be established whenever deemed appropriate by the MC. They will take a goal-oriented, problem-solving approach on any issues that may arise.

Strong and multiple interactions are envisaged among the different organization elements. In general, meetings of a Working Group are expected to take place at *variable geometry,* due to participation of other WG members and/or external experts and/or stakeholders.

The following tables provide a synoptical description of SENESCENCE2030 Working Groups. Tasks, Activities, relevance to the different Objectives and Milestones are also indicated.

WG 1	**Advancement of Knowledge on Cell Senescence and Aging**
Objectives	Relevant to RC01-04
Tasks	T1.1 Exchanging and comparing data on detection and characterisation of senescent cells in normal and pathological tissues; T1.2 Mechanisms of interactions of cell senescence with other hallmarks of aging; T1.3 Compare animal, cellular, organoid models for the study of cell senescence and aging.
Activities	Identify priority areas for: A1.1 further research investigations; A1.2 educational initiatives and high-level training; A1.3 technology and industry development. A1.4 Organise WG1 Meetings A1.5 Organise sections of the annual conferences focused on WG1 themes; A1.6 Contribute to Action's publications as well as to annual and final reports
Milestones	M1.1: WG1 conference (month 10); M1.2 Mid-term report (month 25)

WG 2	**From Knowledge on Senescence to the Impact on Age-Related Diseases**
Objectives	Relevant to RC02-05
Tasks	T2.1 Exploring the role of cellular senescence in predisposing individuals to age-related diseases. T2.2 Investigating the impact of genetics, environment, and overall lifestyle choices on the development of undesirable senescent cells. T2.3 Exploring innovative approaches based on cell senescence research for managing the aging process and age-related diseases.
Activities	A2.1 Identify areas where further efforts are necessary and new gerodiagnostic interventions will be most likely effective in the close future. A2.2 Identify new good clinical practice for prevention, early detection and cure of age-related frailty and disorders; A2.3 WG2 Meetings; A2.4 Organise sections of the annual conferences focused on WG1 themes; A2.5 Contribute to publications, annual and final reports; A.2.6 Contribute to dissemination, exploitation, training schools.
Milestones	M2.1: WG2 conference (month 21); M2.2: Mid-term report (month 25).

WG 3	**The Societal Impact of Cell Senescence Research and Related Policies**
Objectives	Relevant to RC05 and CB01-05
Tasks	T3.1 Examine research on cell senescence in terms of policy perspectives, including regulatory frameworks for clinical trials policies and practices to support the prevention of age-related diseases T3:2 Evaluate, in the contest of the One-Health approach, the potential impact of research on aging promoting healthy behaviors in the aging population across all socio-economic groups. T3.3 Provide recommendations on improving policy design through policy impact evaluation activities

Activities	A.3.1 Comparing met and unmet needs in the geroscience area at the international level, in particular in different EU Member States and COST associated Countries. A3.2 Review machine learning approaches to classify individuals into different exposure profiles or phenotypic patterns. A3.3 Review, at the international level, standardised procedures relevant to wider applications of the results of cell senescence. A.3.4 Review ongoing clinical trials and patents in the area of senotherapy.
Milestones	M3.1: WG3 conference (month 33); M3.2: Mid-term report (month 25).

WG 4	**Dissemination and Public Engagement.**
Objectives	Relevant to CB01, 04, 05
Tasks	T 4.1 Foster educated discussions among policy makers and the general public on novel approaches to preventing, diagnosing, repairing the undesired effects of aging, including age-associated disease. T 4.2 Promote operative interactions of Senescence 2030 with large endeavors related to cell senescence taking place at European and International level. T 4.3 Encourage proposals of novel EU-funded international R&I projects based on cell senescence.
Activities	A4.1 Develop and implement a communication a communication strategy (including website and socials) to raise awareness of cell senescence and its implications for aging and age-associated disease. A4.2 Collect and maintain on the Action website links to educational resources for the general public on cell senescence A4.3 Inform major international policy makers on achievements and acquisitions by WG1-G3 to attract interest and attention on geroscience issues A4.4 Participate in international events with the aim of promoting and attracting attention to SENESCENCE2030 activity and to its general objectives A4.5 Organize in the context of the SENESCENCE2030 Action meetings, round tables dedicated to discussion of training and research opportunities in the geroscience area. A4.6 Contribute to training schools
Milestones	M4.1 Website online (month 6); M4.2 Senescence 2030 Communication Strategic plan

4.1.2. DESCRIPTION OF DELIVERABLES AND TIMEFRAME

During the lifetime of SENESCENCE2030, the following deliverables will be produced (responsible structure and approximate month of delivery are indicated):

Action Strategic-Plan (CG, M3); Annual Reports (AR) on progress regarding implementation of networking activities and development of S&T projects (MC Chair, M12, M24, M36, M48); Reports of WG Meetings (WG1, WG2, WG3, WG4; M12, M24, M36, M48); Report on Educational-Plan including STSM and Training Schools (STSM Committee and STSM Coordinator; M6, M30); Report on Stakeholders mapping, prioritization, and engagement strategy (WG4; M9); "Reports on Action sustainability in progress during the Action" (SC, WG4; M6, M18, M30, M42); Report on Publications co-authored by Action members (MC; M36); Release of SENESCENCE2030 website (SC, WG4; M6); Report on ECIs sessions of Annual Conferences (MC Chair, M16); Report on international R&I Projects or Educational Programs proposed by Action Members as a result of the Action activities (CG and WG4, M36); Report on the involvement of stakeholders and dissemination (SC with WG, M30).

Furthermore, production of the following deliverables is a milestone.

- First major action's Publication (P1). (SC, WG1, WG2, WG3, WG4, M18)
- Second major action's Publication (P2). (SC, WG1, WG2, WG3, WG4, M30)
- Third major action's Publication (P3). (SC, WG1, WG2, WG3, WG4, M42)

Starting from the second year of activity, the Annual Reports by the MC Chair are considered milestones provided that they report at least two co-authored publications acknowledging the Action support, and/or at least one new application to EU funding supporting R&I networks, and/or significant participation of the Action in at least one major event involving stakeholders.

4.1.3. RISK ANALYSIS AND CONTINGENCY PLANS

RISK	**CHANCE**	**IMPACT**	**NOTES**

Inadequate Network Expansion	Low	Low	Systemic actions in the dissemination plan, such as sending information about the Action's activities and invitations to join, will be put in place to increase network expansion persistently.

Low attendance to meetings	Medium	Medium	Meetings will be scheduled in a timely manner, and participants' agreement will be sought. In case of difficulties, attendance profiling will be performed, with an emphasis on giving opportunities to ECIs and aligning meetings with other popular scientific events in the field. Practical results from each meeting will be prioritized.
Difficulties due to busy schedules of health care professionals	Medium	High	For any significant delays, a substitute within the Action will be assigned to the particular task to ensure continuity and progress.
Difficulties due to lower prioritisation from the stakeholders' and policy makers' point of view	Medium	High	Deliverables and milestones are designed to be non-dependent on environmental priorities, but prioritizing cell senescence in European R&D programs is a key task. If challenges arise, a major review of the strategic plan will be undertaken with concerted efforts from the MC and WGs.
Low quality outputs	Medium	High	SENESCENCE2030's openness invites new participants, providing opportunities for contingency plans if low-quality inputs are observed during the implementation.
Low activity and output in local or regional ecosystems	High	Medium	Depending on the issue's nature, the Action MC may establish one or more focus groups, as described in Section 1.1.1, to address and enhance activities in local or regional ecosystems.

4.1.4. GANTT DIAGRAM

	YEAR 1				YEAR 2				YEAR 3				YEAR 1			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
	MC			MC				MC				MC				MC
MC meeting	CG			CG		CG		CG		CG		CG		CG		CG
CG meeting																
Website		G1		G1		G1*		G1		G1*		G1		G1		
WG1 meeting		G2		G2		G2*		G2		G2*		G2		G2		
WG2 meeting		G3		G3		G3*		G3		G3*		G3		G3		
WG3 meeting		G4		G4		G4*		G4		G4*		G4		G4		
WG4 meeting																
STSM			AW				AW				AW				AW	
Annual Workshop			AC				AC				AC				AC	
Annual Conference			SuS				SuS				SuS				SuS	
Summer School			W		W		W		W		W		W		W	
Webinar																
Dissemination					P1				P2				P3			
Publication				AR				AR				AR				AR
Annual Report																

NOTES Activities are in Green, milestones in Magenta; asterisks indicates online meetings; permanent activities are in Brown.

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